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CONSERVATIVE TREATMENT OF OCCLUSIVE ARTERIAL DISEASE

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The steady increase in the number of clinics where internists and surgeons are cooperating closely in an attempt to solve the many problems associated with peripheral vascular diseases constitutes an encouraging index of the care which patients suffering from these conditions will receive in the future.

Although the object of all internists and surgeons may be conceded to be the ultimate benefit of the patient and his restoration to a life as nearly normal as possible, the training of the two groups tends toward different philosophic and technical approaches to this objective. This gulf is widened by isolation and narrowed by close association. The problems involved will receive sounder consideration as a result of continuous interplay of surgical and medical opinion, and no clinic devoted to this field can be considered adequate which does not make this inevitable.

In general, medical care of the extreme forms (ulceration and gangrene) of vascular disease rests on conservative therapy, i. e., on allowing epithelization or self amputation to take place. Surgical care has been directed toward quick healing and, this failing, toward some radical procedure, such as amputation or ganglionectomy. Obviously, in instances of infection which spreads rapidly in spite of attempts to control it and which shows evidence of toxic absorption and sepsis, most workers will agree that amputation is the logical recourse. When the lesion is chronic rather than acute the problem is more equivocal. The surgeons call attention to the long period of inactivity of the patient and the economic loss involved in maintaining a conservative regimen for a period varying from three to eight or nine months, when with amputation the period could be reduced to six weeks of hospitalization. They point out also that many patients fail to get better despite conservative therapy, and are eventually treated by amputation. The internists, on the other hand, ask whether most patients would not

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prefer to wait a few extra months for preservation of an extremity, even an imperfect one. They ask also how many months must elapse after the patient leaves the hospital before he is able to get about and especially before he is able to use an artificial limb. What, they ask, of the 40 to 60 per cent of arteriosclerotic patients who, having had an amputation, never learn to use an artificial limb? These questions must be considered with each patient in relation to many additional factors, including the type and extent of the disease, the age of the patient, the potential capacity for future activity, the associated pain, the course and complications of the disease and the results of clinical, laboratory and roentgen studies. In the ideal service these factors are reviewed jointly by the medical and the surgical group in an endeavor to determine the proper course to pursue.

If conservative therapy is selected for a patient with occlusive arterial disease, the choice of methods is wide; this indicates that, although several may be worth while, there is no specific cure. The immediate object of the various forms of treatment is improvement of the circulation to the involved area by vasodilation of the active vessels, widening of the collateral channels and reestablishment of canals through old occluded vessels. An endeavor will be made to describe such procedures as seem to warrant discussion, with an attempt at evaluation of each in the light of the experience obtained at the clinic for vascular disease of the New York Post-Graduate Medical School and Hospital and the experience of reliable workers elsewhere as described in their published reports or in personal communications. It should be recognized that knowledge in this relatively newly explored field is in a state of flux and that any such attempt at evaluation is curbed by difficulties. The apparent truth of today may be the error of tomorrow.

Since the most important occlusive vascular diseases are arteriosclerosis obliterans and thromboangiitis obliterans and since much of the present day therapy has been used for both, my discussion will apply chiefly to these conditions, specific applications being pointed out when indicated.

REST

Whenever there is ulceration, gangrene, marked progressive discoloration, pronounced and sudden local coldness or severe "rest pain," the involved extremity should be placed at relative rest. The level selected for maintenance of the most satisfactory circulation possible under the circumstances has been shown by Reid [1] to be very important. If the extremity is kept in a dependent position for too long, the veins become engorged, and the engorgement results in increased

1. Reid, N. R.: A General Consideration of Blood Supply in the Practice of Medicine and Surgery, South. M. J. **26**:107 (Feb.) 1933.

venous and capillary pressure and stagnation of blood. If, on the other hand, the extremity is kept elevated, it becomes blanched and bloodless in appearance and the tissues become ischemic, since the force within the diseased arteries is usually insufficient to carry fresh blood to the tips of the extremity. Such elevation, when prolonged, has been a frequent cause of amputation in the past.

Between these extremes is a level which appears to be the most efficient from the standpoint of proper blood supply. This is the point at which the superficial veins fill to such an extent that they project slightly above the level of the skin. It will usually be found from 3 to 6 inches (7.5 to 15 cm.) below the level of the heart. At this level gravity assists the flow of arterial blood into the limb, and the blood is not retarded in its return by too greatly increased venous back pressure.

Rest should be continued until the lesion is healed or the acute episode is completely over, after which activity should be undertaken guardedly and under observation until the return of the condition is considered unlikely. Specific vascular exercises should be the only exceptions to this.

ACTIVE VASCULAR EXERCISES

1. *Buerger's Exercises.*—Various slight modifications of the exercises described by Buerger [2] have been accepted and used widely to exercise the vascular tree, to clear away stagnant blood and to stimulate the opening of the collateral vessels. A suggested technic is as follows: The patient rests on his back in bed. An incline beginning at the level of the hips is built up on the foot of the bed. The angle of inclination should be 45 to 60 degrees. Pillows or the back of an inverted chair may be used. The legs are (*a*) elevated on this incline for one to three minutes, (*b*) lowered over the edge of the bed for three to ten minutes and (*c*) rested at bed level (horizontally) for five to ten minutes. This cycle is repeated five or ten times twice or three times a day. Color changes (blanching on elevation and rubor on dependency) clearly indicate that blood is draining from and filling the vascular tree. The timing should be such that neither blanching nor rubor is marked for more than one minute.

2. *Allen's Exercises.*—Allen [3] has suggested a modification of this procedure which is helpful if the feet are not too painful. While the legs are hanging over the edge of the bed, further exercises are performed as follows: (*a*) The feet are extended downward; (*b*) the feet are raised by flexion at the ankle joint, not by raising the legs; (*c*)

2. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

3. Allen, A.: Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, Ann. Surg. **92**:931 (Nov.) 1930.

the toes are turned inward as far as possible; (*d*) the toes are turned outward as far as possible; (*e*) the toes are spread with the feet in normal position, and (*f*) the toes are "closed." This should be repeated during the dependent phase of each cycle.

CARE OF THE EXTREMITIES

Once the diagnosis is made, whether an acute condition is present or not, meticulous care must be taken of the extremities involved. If free from open lesions they should be washed carefully at least three times a week with warm (not with hot) water and rubbed thoroughly thereafter with olive oil or hydrous wool fat to keep the skin soft. Corns and calluses should be carefully softened with salicylic acid ointment. Paring should be discouraged except in the most expert hands. The nails should be cleansed and pared with extreme care to avoid production of minor lesions requiring surgical treatment. Trauma and frostbite must be avoided. Shoes must be soft and must fit well, to avoid abrasion. Socks should be of soft wool, to cushion the feet.

ABSTINENCE FROM TOBACCO

It is now generally recognized that the use of tobacco in the presence of impaired circulation is inadvisable. It was first noticed by Silbert [4] (among others) that in cases of thromboangiitis obliterans smoking is a markedly aggravating, if not the most important etiologic, factor. Most clinics subscribe to this theory, at least in reference to aggravation. Experimental studies by Maddock and Coller,[5] Barker,[6] Wright and Moffat [7] and Lampson [8] have established the fact that the smoking of tobacco usually produces diminution of the blood supply to an extremity, normal or otherwise, by constriction of the peripheral arterioles, as determined by thermocouple readings and by capillary microscopic and plethysmographic studies. That this is not due to deep respiration as has been claimed by Mulinos and Shulman [9] can

4. Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): Treatment of Five Hundred and Twenty-Four Cases by Repeated Intravenous Injections of Hypertonic Salt Solution; Experience of Ten Years, Surg., Gynec. & Obst. **61**:214 (Aug.) 1935.

5. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, Ann. Surg. **98**:70 (July) 1933.

6. Barker, N. W.: Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet., Mayo Clin. **8**:284 (May 10) 1933.

7. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral Vascular System, J. A. M. A. **103**:318 (Aug. 4) 1934.

8. Lampson, R. S..: A Quantitative Study of the Vasoconstriction Induced by Smoking, J. A. M. A. **104**:1963 (June 1) 1935.

9. Mulinos, M. G., and Shulman, I.: Vasoconstriction in the Hand from a Deep Inspiration, Am. J. Physiol. **125**:310 (Feb.) 1939.

be demonstrated by comparing the depth of respiration necessary to produce slight drops in the temperature of the finger tips as compared with the profound drops often caused by smoking with only mild or moderate inhalation.

An attempt by Harkavy and his co-workers [10] to place the effect of tobacco in thromboangiitis obliterans on an allergic basis has been opened to serious question by the work of Trasoff, Blumstein and Marks [11] and that of Wescott and Wright.[12]

Thus far, the only established mechanism involved is the physiologic one of constriction of the small arteries and arterioles. Even for the arteriosclerotic patient with already impaired circulation this is sufficient to interdict its use. Although spasm of the sclerotic vessels is not considered important, one must remember that the life of the tissues frequently depends on the collateral vessels, that these are usually not sclerotic and that they may be constricted by smoking. If, for example, the circulation in an extremity is already impaired to a fraction of its former potential, i. e., to the point at which life of the tissue is endangered, the deciding factor may be further constriction of the vessels, reduction of circulation and production of gangrene. This principle operates in all degrees, and in my opinion, indicates that patients with definitely impaired circulation from arteriosclerosis or any other cause should completely abstain from the use of tobacco.

The clinical evidence is even stronger in the cases of thromboangiitis obliterans. In my experience and that of my associates, good results are to be expected from the general treatment outlined here provided the patient will completely stop smoking. The only 3 patients in our series of 100 cases of thromboangiitis obliterans observed since 1931 on whom major amputations were performed continued to smoke surreptitiously even though warned many times of the dire consequences. Each of these 3 patients lost one leg. Patients who steal an occasional smoke usually have ulcers which are slow to heal, continue to ooze and look inflamed. If an ulcer has been healing nicely and it suddenly enlarges and begins to look inflamed, careful questioning will usually elicit a confession of a relapse to smoking. Numerous patients whose ulcers have been healed for from six months to several years have returned with a new ulcer and an admission that they had resumed smoking, after which, within

10. Harkavy, J.; Hebald, S., and Silbert, S.: Tobacco Sensitiveness in Thromboangiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **30**:104 (Oct.) 1932.

11. Trasoff, A.; Blumstein, G., and Marks, M.: Immunologic Aspect of Tobacco in Thrombo-Angiitis Obliterans and Coronary Heart Disease, J. Allergy **7**:250 (March) 1936.

12. Wescott, F. H., and Wright, I. S.: Tobacco Allergy and Thromboangiitis Obliterans, J. Allergy **9**:555 (Sept.) 1938.

a few days or weeks, the pain and the ulcer returned. Results of therapy in this disease depend on the edict: "Absolutely no smoking, now and forever!"

ALCOHOL

In contrast, the action of alcohol on the peripheral arteries is definitely vasodilating. In experiments performed in this laboratory,[13] the rise in temperature of the tips of the extremities after ingestion of 60 to 90 cc. of whisky has been as great as 9 to 12 degrees (F.), depending in part on the condition of the vessels and the control temperature prior to the experiments. I feel, therefore, that the use of whisky or other spirituous liquors is indicated in the treatment of organic occlusive disease of the peripheral vascular system. There is general agreement in this at present among most of the leading clinics for vascular disease. The dose depends on the severity of the condition. With impending or actual gangrene the patient should receive enough to keep the peripheral vessels as much dilated as possible. In many cases he should be kept slightly inebriated during the critical period. This sometimes requires 30 to 60 cc. (1 to 2 ounces) of whisky every four hours or more frequently. This may be tapered down as the emergency subsides to 30 to 60 cc. once or twice a day, which is the dose usually recommended in cases of nonacute involvement. As Brown, Allen and Mahorner[14] pointed out, in addition to its vasodilatory properties whisky may control the pain of peripheral vascular disease in some cases more satisfactorily than morphine.

Unless there are definite contraindications, such as severe diabetes, gastric ulcer or alcoholism, I feel that patients with arteriosclerosis obliterans should have some alcoholic beverage each day for the remainder of their lives.

BATHS

The proper use of baths constitutes a definite contribution to the treatment of occlusive vascular disease. Baths may be grouped under several headings, as follows:

1. *Contrast Baths.*—Perhaps the most generally used bath for this type of condition is the contrast bath. Two containers are placed side by side. They should be deep, reaching to the patient's knee. In one, water at 40.2 C. (105 F.) is placed. In the other, water of "tap water temperature," 15.5 to 20.1 C. (60 to 70 F.), is used. The legs are placed first in one and then in the other at intervals varying from one to three minutes. The last immersion should always be in the hot water. My

13. Wright, I. S.; Poindexter, C., and Van Dellen, T.: The Vaso-Dilating Effects of the Ingestion of Spiritous Liquors, unpublished data.

14. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thromboangiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

associates and I have suggested seven alternations, beginning and ending with hot water. This treatment should be given once or twice a day, depending on the condition of the extremity. The theory is that the patent vessels are exercised by producing alternate vasoconstriction and vasodilation. There are, however, several objections to this type of bath, which have resulted in our abandoning its use. First, the best containers reach only to the knees. The blockage may be far above that level, so that, although the contrast baths may produce different metabolic demands, the ability to respond may not be realized at the level of the stimulus. Second, when already damaged vessels are forced into sudden vasospasm they may remain closed, complicating the picture considerably. Third, in our experience there is often severe pain during the cold phase, perhaps due to cramping or to ischemia. We have therefore adopted a modification of the long-used sitz bath for this purpose.

2. *Sitz Baths.*—The patient sits in a tub containing at least 12 inches (30 cm.) of water at a temperature of 37.8 to 40.2 C. (100 to 105 F.) for twenty to thirty minutes at least once a day. This overcomes all of the objections to the contrast bath. (Theoretically it does not exercise the small vessels as well.) The heat extends high enough to activate the collateral arteries from the trunk and also the femoral arteries. No cold water being involved, the risk of sudden permanent occlusion or of severe pain is minimized. If water of this temperature appears to cause discomfort, the temperature should be reduced to 34.4 to 36.7 C. (94 to 98 F.). This type of bath is not, of course, suitable for patients with open ulcers or gangrene, because of the risk of infection.

3. *Whirlpool Baths.*—Whirlpool baths, if available, may further stimulate the circulation, the motion of the water being especially helpful in the presence of chronic low grade ulceration. The temperature of the water should be about the same as for the sitz bath. Whirlpool baths usually have the objection of not extending high enough on the limb.

4. *Soaks.*—Wet dressings have largely been abandoned in this clinic because of their tendency to cool even under the most favorable conditions. This produces vasoconstriction and thus does more harm than good by defeating the chief aim, that of improving the circulation to the dying cells. In their place, for ulcerated or gangrenous extremities we use soaks of boric acid solution or physiologic solution of sodium chloride at 35.7 to 37.8 C. (96 to 100 F.). These may be applied two or three times daily for fifteen to thirty minutes. After each soak the foot is removed, dried carefully and placed under a warm lamp cradle at 33.2 to 35.4 C. (92 to 96 F.) to prevent chilling. The object should be to allow proper drainage by softening and cleaning away crusts which tend to lock in infection, but once infection is under control attempts

should be steadily made to produce a dry lesion rather than a wet, macerated one. Healing is made more rapid and the danger of infection is reduced when the lesion is dry.

HEAT

1. *Local Heat.*—The problem of heat is one of great importance in the handling of arteriosclerosis and thromboangiitis obliterans. It is probable that in the past heat has done more harm than good, because of improper use. Properly handled, it tends to reproduce normal temperature. The normal surface temperature rarely exceeds 39.9 to 35.6 C. (93 to 96 F.). In order to achieve this and hence stimulate normal metabolic processes the temperature of the environment should approximate that level. My associates and I therefore use thermostatically controlled heat cradles [15] which keep the temperature between 34.4 and 35.7 C. (94 and 96 F.). By careful watching and the use of a thermometer an equal distance between the lamp and the extremity it is possible to use ordinary light bulbs, but the factor of error is great, and the disease in many cases has been greatly aggravated by overheating. As Starr [16] has pointed out, increasing the metabolic demands beyond the capacity of the supplying arteries leads to increasing gangrene. Controlled heat within these limits is, in our opinion, the only safe form of heat for use in this condition. The local use of heat lamps, diathermy or short wave mechines is to be condemned. I have seen in consultation many patients with severe ulceration, massive necrosis or gangrene which appeared to have been precipitated by such measures; 7 of these patients lost their legs, and 2 died—not primarily as a result of vascular disease but rather of the results of the misapplied treatment. I have emphasized this previously.[17]

2. *Reflex Heat.*—Using a modification of the principle employed by Gibbon and Landis,[18] my associates and I have used reflex heat as a therapeutic measure as well as to determine the potential vasodilatation of the vascular tree. After trying several approaches, we have found the simplest effective technic to be merely the application of an electric heating pad over the abdomen for thirty to sixty minutes once or twice a day. Optimum dilatation of the vessels of the extremities (considering the disease present) is thus obtained. Greater heat (the maximum com-

15. Those used by us were made by the Valverde Laboratories, of New York.

16. Starr, I., Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, Proc. Soc. Exper. Biol. & Med. **29**:166 (Nov.) 1931.

17. Wright, I. S.: Physical Therapy in Peripheral Vascular Disease, Arch. Phys. Therapy **19**:161 (March) 1938.

18. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in Lower Extremities in Response to Immersing Forearms in Warm Water, J. Clin. Investigation **11**: 1019 (Sept.) 1932.

patible with the safety and comfort of the patient) should be used with this device, as the dilation occurs from the proximal toward the distal ends of the extremities. If diathermy, short wave therapy or infra-red rays are to be used for these conditions, their application should be to the trunk to produce reflex vasodilatataon.

Wilkins, Doupe and Newman [19] have shown by means of plethysmographic studies of the fingers that the increase in blood flow resulting from local heat is not as great as that produced by warming the body.

TYPHOID VACCINE

In our experience typhoid vaccine given intravenously in the manner to be outlined is of great value in the treatment of thromboangiitis obliterans. We have been cautious in its use for arteriosclerosis and have recommended it only when all other methods have proved inadequate to control progression toward gangrene. In a few cases it has been possible to reverse the process, producing marked improvement, but, although we have had no accidents, we are inclined to fear coronary or cerebral thrombosis as a complication.

The action of typhoid vaccine is nonspecific, probably depending purely on vasodilation of the available functioning main and collateral vessels supplying the limb. The use of nonspecific foreign protein therapy was first suggested by Goodman and Gottesman [20] in 1923 and was advocated by Brown,[21] Allen and others. It is now one of the most widely accepted forms of therapy for thromboangiitis obliterans. Until 1931 Brown and Allen used triple typhoid vaccine (typhoid and paratyphoid A and B strains, Lederle). Barker [22] in 1931 described "typhoid H" antigen (Lilly), a fraction of the typhoid bacterium prepared by emulsifying the organisms in sodium chloride solution and subsequently killing them with 0.5 per cent phenol. The results seemed better than with the triple typhoid vaccine, and the untoward effects were less.

My associates and I have used with good results and minimal untoward effects a typhoid vaccine prepared especially for this purpose according to our direction.[23] It is prepared from typhoid bacilli exclusively and is diluted to the strength of 100,000,000, organisms per cubic

19. Wilkins, R. W.; Doupe, J., and Newman, H. W.: The Rate of Blood Flow in Normal Fingers, Clin. Sc. **3**:403 (Dec.) 1938.

20. Goodman, C., and Gottesman, J.: Pain and Its Treatment in Thromboangiitis Obliterans, New York M. J. **117**:774 (June 20) 1923.

21. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87**:379 (Aug. 7) 1926.

22. Barker, N. W.: Results of Treatment of Thrombo-Angiitis Obliterans by Foreign Protein, J. A. M. A. **47**:841 (Sept. 19) 1931.

23. The vaccine was prepared by the Kirk Biological Laboratories, of Bloomfield, N. J.

centimeter. This dilution permits more accurate measurements of the dose than do the more concentrated solutions in routine use. Severe reactions have been caused in the past by attempts to measure accurate doses of typhoid vaccine from too concentrated a suspension, the fact being forgotten that suspensions tend to settle and vary in concentration unless they are shaken thoroughly before use. The risk is minimized by using low concentrations and shaking well. The procedure used is as follows. The first dose is 5,000,000 organisms. Injections are given every three days, provided that the effect of the preceding dose has completely worn off. The object is to obtain a rise in oral or rectal temperature of 2 or 3 degrees F. (1 or 2 degrees C.) without a chill. Although usually a slight drop in surface temperature precedes the rise, this is inconsequential if no chill occurs. The rise in surface temperature of the tips of the extremities with this fever is from 3 to 4 degrees C. (4 to 6 degrees F.), but of course it is affected by the degree of occlusion of the total arterial supply to the limb, including the collateral vessels.

When a dose of 5,000,000 organisms fails to produce a satisfactory fever, the dose is increased to 10,000,000 and kept at that level as long as the reactions are satisfactory. Increases of 3,000,000 to 5,000,000 organisms are made whenever the effects of the preceding dose are inadequate; otherwise the dose is repeated at the same level. If the temperature goes above 39.5 C. (103 F.) and a chill occurs, the next dose is decreased by 3,000,000 to 5,000,000. Doses have been increased up to 200,000,000 or more, but with most patients a top level of 70,000,000 to 130,000,000 seems to be reached, and administration can be continued indefinitely at that level. Proceeding carefully in this manner, with over 12,000 injections we have had no serious untoward effects attributable to the treatment. During acute infection or other serious illness this treatment has been suspended.

The results following the use of this technic have been gratifying. Relief of the pain associated with small ulcers has occurred after the first, second or third injection, and rapid healing has taken place. The major gangrenous processes naturally respond more slowly, but the results appear to us to be more rapid than are those of intravenous administration of saline or citrate solutions. These methods will be discussed.

INTRAVENOUS ADMINISTRATION OF SALINE SOLUTION AND OTHER SOLUTIONS

Since the observation of Mayesima [24] that the viscosity of the blood is increased in thromboangiitis obliterans, various solutions have been used on the theory that reduction of the viscosity would have a favorable

24. Mayesima, J.: Klinische und experimentelle Untersuchungen über die Viskosität des Blutes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:413, 1911-1912.

effect on the course of the disease. Koga [25] in 1913 was the first to introduce intravenous therapy for the treatment of thromboangiitis obliterans, using physiologic solution of sodium chloride in some cases and Ringer's solution in others. Willy Meyer [26] in 1916 was the first American to adopt this method, using the same solutions. Ginsburg [27] in 1917 and Steel [28] in 1921 used sodium citrate. Various other solutions have been tried, but the most widely used at present is hypertonic (3 to 5 per cent) solution of sodium chloride as introduced by Silbert [29] in 1926. The dose is usually 300 to 400 cc. of 3 per cent solution given intravenously three to seven times a week. The results have repeatedly been reported on favorably by Silbert [30] and by Samuels.[31] The action of the substance has not been clearly demonstrated, although various explanations have been advanced, namely, reduced viscosity, increased pulse volume and vasodilation. A uniform increase in the surface temperature is not observed.

After study, intravenous injections of large volumes of saline or citrate solution has been abandoned by numerous workers in favor of the other forms of therapy outlined here. In my experience and that of my associates, the use of typhoid vaccine results in a quicker response, prompter relief of pain and more satisfactory healing.

Hypertonic saline solution (especially the 5 per cent solution) may produce venous thrombosis, chills and hepatitis. Although we do not consider it the treatment of first choice, there may be patients with thromboangiitis obliterans for whom it should be tried when typhoid vaccine is contraindicated or when response to it does not appear satisfactory. The use of this substance has thus far no sound theoretic basis in the treatment of arteriosclerosis and is not recommended at this time.

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25. Koga, G.: Zur Therapie der Spontangangrän an den Extremitäten, Deutsche Ztschr. f. Chir. **121**:371, 1913.

26. Meyer, W.: The Conservative Treatment of Gangrene of the Extremities Due to Thrombo-Angiitis Obliterans, Ann. Surg. **63**:28 (March) 1916.

27. Ginsburg, N.: A Consideration of the Treatment of Peripheral Gangrene Due to Thrombo-Angiitis Obliterans, Am. J. M. Sc. **154**:328 (Sept.) 1917.

28. Steel, W. A.: Sodium Citrate Treatment of Thrombo-Angiitis Obliterans, J. A. M. A. **76**:429 (Feb. 12) 1921.

29. Silbert, S.: The Treatment of Thrombo-Angiitis Obliterans by Intravenous Injection of Hypertonic Salt Solution, J. A. M. A. **86**:1759 (June 5) 1926.

30. Silbert, S.: Thrombo-Angiitis Obliterans: Results of Treatment with Repeated Injections of Hypertonic Salt Solution, J. A. M. A. **94**:1730 (May 31) 1930; footnote 4.

31. Samuels, S.: Gangrene Due to Thrombo-Angiitis Obliterans, J. A. M. A. **102**:436 (Feb. 10) 1934.

SODIUM CITRATE, RINGER'S SOLUTION AND INSULIN

The use of sodium citrate, Ringer's solution and insulin for the treatment of thromboangiitis obliterans and arteriosclerosis is being given up in most clinics, being confined to a few scattered institutions. I therefore feel that further discussion of these substances is not indicated.

VASODILATING DRUGS

Numerous drugs have been used in the treatment of thromboangiitis obliterans and arteriosclerosis obliterans on the basis of their vasodilating powers. The more common of these may roughly be divided into:

1. The nitrites and allied compounds
2. The theobromines, theocalcine (a mixture of calcium theobromine and calcium salicylate) and allied compounds
3. The choline compounds
4. Papaverine

After years of study, both clinical and experimental, with all of these substances it seems fair to state that the value of their use singly or collectively in the treatment of these conditions is relatively limited.

Briefly, the action of the nitrites is too fleeting, and the dilatation as it affects the vessels of the extremities is observed with difficulty.

The action of theobromine and its allied compounds in the usual doses is unreliable and doubtful.[32]

The action of certain of the choline compounds, although of established value in the treatment of certain diseases of the peripheral circulation, such as varicose ulcers, appears to be of no value in the treatment of arteriosclerosis and to be useful only rarely in the treatment of thromboangiitis obliterans.[33]

Papaverine has been advocated for the relief of sudden occlusion and for its general vasodilating qualities.[34] In a recent study Littauer and

32. McGovern, T.; McDevitt, E., and Wright, I. S.: Theobromine Sodium Salicylate as a Vaso-Dilator, J. Clin. Investigation **15**:11 (Jan.) 1936.

33. Saylor, L.; Kovacs, J., and Wright, I. S.: The Pharmacological and Therapeutic Effects of Certain Choline Compounds, Am. Heart J. **11**:53 (Jan.) 1936. Saylor, L.; Kovacs, J.; Duryee, A. W., and Wright, I. S.: Treatment of Chronic Varicose Ulcers by Means of Acetyl-Beta-Methylcholine Chloride Iontophoresis, J. A. M. A. **107**:114-117 (July 11) 1936.

34. Denk, W.: Zur Behandlung der arteriellen Embolie, München. med. Wchnschr. **81**:437 (March) 1934. Allen, E. V., and MacLean, A. R.: Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride, Proc. Staff Meet., Mayo Clin. **10**:216 (April 3) 1935. deTakáts, G.: The Use of Papaverine in Acute Arterial Occlusions, J. A. M. A. **106**:1003 (March 21) 1936.

I [35] have found its vasodilating effects to be highly unreliable and not nearly so marked as the effect of simple reflex heat. The relaxing effect of papaverine and other opiates and the value of this relaxation are undoubted. Such preparations should be used wisely and with the possibility of ultimate habituation in mind, although this danger has proved to be a serious factor only once in our experience. Morphine should be used only as a last resort, because of the familiar objections of nausea, distention and habituation.

The long-standing use of potassium iodide in the treatment of arteriosclerosis merits its mention here, although clinically I have been unconvinced of its value. Animal experiments have seemed to demonstrate that it will prevent the actual laying down of cholesterol. This has not, however, been proved to be a process comparable to arteriosclerosis in man.

TISSUE EXTRACTS

The therapeutic use of various tissue extracts was stimulated by the studies of Frey and Kraut [36] and Gley and Kisthinios [37] and in the United States by the work of Wolffe [38] Elliot and Nuzum,[39] Barker, Brown and Roth,[40] Duryee [41] and others. Although at first emphasis was directed toward the effect of these extracts on the anginal syndrome, this proved difficult to evaluate, and more recently increasing interest has developed in the more easily measured response of the syndrome of intermittent claudication to their use. During the past six years my associates

35. Littauer, D., and Wright, I. S.: The Questionable Value of Papaverine Hydrochloride in the Treatment of Peripheral Vascular Disease, Am. Heart J. **17**:325 (March) 1939.

36. Frey, E. K., and Kraut, H.: Ueber einen von der Niere ausgeschiedenen, die Herztätigkeit anregenden Stoff, Ztschr. f. physiol. Chem. **157**:32, 1926; Ein neues Kreislaufhormon und seine Wirkung, Arch. f. physiol. Chem. **175**:97, 1928. Frey, E. K.: Kreislaufhormon und innere Sekretion, München. med. Wchnschr. **76**:1951 (Nov. 22) 1929.

37. Gley, P., and Kisthinios, N.: Recherches sur la substance hypotensive du pancréas, Presse méd. **37**:1279 (Oct. 2) 1929.

38. Wolffe, J. B.: The Therapy of Tissue Extract ("Desympatome"), Tr. Am. Therap. Soc. **31**:31, 1931; Further Studies on Tissue Extract No. 568 (Desympatone), ibid. **34**:163, 1934.

39. Elliot, A. H., and Nuzum, F. R.: The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulator Hormone of Frey, J. Pharmacol. & Exper. Therap. **43**:463 (Nov.) 1931; Pancreatic Extract in the Treatment of Angina Pectoris and Intermittent Claudication, Arch. Int. Med. **49**:1007 (June) 1932.

40. Barker, N. W.; Brown, G. E., and Roth, G. M.: Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), Am. J. M. Sc. **189**:36 (Jan.) 1935.

41. Duryee, A. W.: Tissue Extract in the Treatment of Peripheral Vascular Disease, Tr. Am. Therap. Soc. **35**:124, 1935.

and I have been using various extracts prepared from the pancreas, heart, skeletal muscle and liver. Certain of these proved on physiologic and clinical studies to be active, but they were for the most part rather crude, poorly standardized, high in protein content and painful to inject. Various fractions have been tried, and for the past year and a half we have been using a deproteinated pancreatic extract.[42] It is a colorless saline solution of a chemically purified, protein-free, nitrogenous fraction derived from an acid alcohol extract of beef pancreas. Physiologic tests show that it is apparently free from insulin, histamine and acetylcholine. It contains approximately 2.5 per cent of solids, including 0.25 per cent of nonprotein nitrogen, 0.9 per cent of sodium chloride and 0.25 per cent of phenol as a preservative. It is adjusted to a p_H of 6.5 to 6.8.

It is assayed by comparing its effect with that of a standard preparation on the arterial blood pressure of anesthetized dogs. This standard preparation is of such potency that in a large series of dogs 1 cc. produces an average lowering of arterial blood pressure equal to that produced by 0.01 mg. of epinephrine in the same dogs. The standard preparation is preserved by the lyophil process and stored in the dried state at 5 C. Each new lot of deproteinated pancreatic extract is standardized by comparing its depressor effect with that of a solution of the standard preparation on the normal and on the atropinized dog. The physiologic action of each lot is also studied by means of the heart-blocking effect in mice. Two cubic centimeters of "depropanex" is injected into white female mice, and an electrocardiograph is used to ascertain whether heart block occurs. The material is injected intraperitoneally and should not cause death from heart block in any of at least 3 mice within fifteen minutes.

A preliminary report of its effects on intermittent claudication in man, measured by an ergometer and by walking ability as measured in blocks (less accurate), has recently appeared (Fisher, Duryee and Wright[43]). Controlled ergometric tests were continued to the point of production of such pronounced pain that the patient was forced to stop. After the length of time necessary for this had been rechecked, an injection of 3 cc. of deproteinated pancreatic extract was given. Thirty minutes later another ergometric test was made. The results of this series of experiments were as follows: Of 8 patients with untreated uncomplicated arteriosclerosis obliterans, 6 showed lengthening of the claudication time; of 5 patients with untreated but complicated arteriosclerosis, 4 showed improvement, and of 14 patients previously treated (for complicated and uncomplicated conditions) 13 showed improvement

42. This substance, "depropanex," was supplied by Sharp and Dohme.

43. Fisher, M. M.; Duryee, A. W., and Wright, I. S.: Deproteinated Pancreatic Extract (Depropanex) Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, Am. Heart J. **18**:425 (Oct.) 1939.

after these initial studies. The improvement after the first injection was fleeting, the effect having worn off within twenty-four hours. Injections of saline solution were given as controls to each patient (without his knowledge), with absolutely negative results. The lengthening of the claudication time may be found in detail in the original paper. The average time prior to the injections ranged from one minute and twenty-six seconds to one minute and forty-three seconds in the various groups. In the half-hour tests the time averaged more than three minutes and one second. After ten or more such injections given intragluteally three times each week the effects were more pronounced and more prolonged as measured on the ergometer. This coincided with the improvement in walking ability reported by the patients.

In a purely clinical study of 100 patients who were followed for four to six months while they received triweekly injections, 74 reported definite clinical improvement; 26 failed to show sufficient improvement to warrant continued use of the extract. A warning should, however, be issued against accepting such clinical studies without proper weighing of the facts. Certain of the patients had been previously treated with a regimen for vascular disease, and this furnished a valuable control period. In other instances, however, as the patient had been recently placed on such a regimen, the improvement may have been partly due to the regimen alone or may have been merely the occasional remission which may occur spontaneously in this condition. No untoward effects have been noted in more than a thousand injections. We have given 48 to 100 cc. of the substance intravenously to rabbits before producing death, whereas 4 to 15 cc. of the former tissue extracts produced collapse and even death. We have given 3 cc. intravenously to 20 patients, with no ill effects. Although we do not advocate this method of administration at present, it serves as an indication of the relative nontoxicity of the extract.

The mechanism of the action of pancreatic tissue extracts has never been satisfactorily explained, although a hormonal or replacement action similar to that of insulin is popularly assumed at present. Assay methods with animals (in which an antagonistic action to epinephrine has been demonstrated) indicate a factor of vasodilatation. This effect has not, however, been noted in man. My associates and I are engaged in studies which may clarify this problem. Some light may be shed on it by certain preliminary studies conducted by us and dealing with the effect of deproteinated and other pancreatic extracts on the experimental production of atherosclerosis in rabbits.[44] The results will be reported in detail elsewhere, but (in summary) four groups of rabbits have been studied, with the results given in tables 1 and 2.

44. Fisher, M. M.; Wright, I. S.; Member, S., and Duryee, A. W.: Unpublished data.

The animals were killed in from four to sixteen weeks. The data in the tables were obtained at autopsy.

The deposition of cholesterol to produce atherosclerosis of the aorta is seen to be markedly retarded by the use of pancreatic tissue extracts.[45] The extracts do not prevent the deposit of fat in the liver. It should

TABLE 1.—*Gross Atherosclerosis of the Aorta and Deposits of Fat in the Liver*

Group		Grade (1 to 4+)										Average
1a (10 control rabbits; regular purina chow)‡	Aorta	0	0	0	0	0	0	0	0	0	—	0
	Liver	0	0	0	0	0	0	0	0	0	—	0
2a (6 rabbits; regular purina chow + 3 cc. pancreatic extract given intramuscularly 3 times per week)	Aorta	0*	0†	0†	0†	0*	0*	..	..	..	..	0
	Liver	0	0	0	0	0	0	..	..	..	..	0
1b (7 rabbits; regular purina chow + 1 Gm. cholesterol 3 times per week)	Aorta	4+	3+	4+	4+	4+	4+	4+	..	..	..	3.9+
	Liver	4+	±	4+	4+	4+	4+	4+	..	..	..	3.5+
2b (6 rabbits; regular purina chow + 1 Gm. cholesterol 3 times per week and 3 cc. pancreatic extract given intramuscularly 3 times per week)	Aorta	3*	0†	0†	0†	0*	0*	..	..	..	..	0.5
	Liver	4+	4+	3+	4+	2+	3+	..	..	..	..	3.3+

* Grant's pancreatic hormone, lot 66. This is a pancreatic extract similar in many respects to the former pancreatic tissue extract no. 568 of Sharpe and Dohme. It is free from insulin but not from protein. It has a favorable effect on the syndrome of intermittent claudication. It is prepared by the Grant Chemical Company of Philadelphia and New York.

† Deproteinated pancreatic extract.

‡ This preparation is made by the Ralston Cereal Company, of St. Louis. It is a mixture of grains and alfalfa hay supplemented by vitamins and minerals. It is said to contain iodized salt, but the amount of iodine present seems to be very small, since it in no way interfered with the disposition of cholesterol in the arteries of any of the control animals fed cholesterol.

TABLE 2.—*Cholesterol Content of the Aorta at Autopsy*

Group	Cholesterol, Gm. per 100 Cc.									Average
1a	0.444	0.420	0.400	0.470	0.590	0.360	0.360	0.750	0.460	0.4726
2a	0.748*	0.456†	0.288†	0.710†	0.205*	0.191*	.....	.....	.....	0.4330
1b	7.610	1.217	2.052	2.233	10.791	7.568	15.441	.....	.....	6.7017
2b	3.150*	1.130†	0.969†	0.742†	0.616*	0.438*	.....	.....	.....	1.2089

* Grant's pancreatic hormone, lot 66.
† Deproteinated pancreatic extract.

be recognized, however, that this type of atherosclerosis, although similar, has not been proved to be exactly identical to human senile atherosclerosis and also that certain other substances, including lipocaic,[46] have been reported to have similar properties. Studies of the blood

45. This has been previously observed by Samuelson, who used other pancreatic extracts.

46. Huber, M. J.; Broun, G. O., and Casey, A. E.: Prevention of Cholesterol Arteriosclerosis in Rabbits by Use of Pancreatic Extract (Lipocaic), Proc. Soc. Exper. Biol. & Med. **37**:441 (Dec.) 1937.

cholesterol were also made. The results were not striking, although some degree of temporary lowering of the level of cholesterol was noted, and the general average for the series was lower for the rabbits fed cholesterol and receiving tissue extract than for those receiving cholesterol but no tissue extract. More extensive animal and clinical studies will be necessary for final evaluation of this substance. Other fractions may prove more potent. At present the one in use appears to be nontoxic; its administration is practically painless, and it is of some value in the treatment of certain patients with the syndrome of intermittent claudication. Further studies regarding the mechanism of its action and the clinical problems of dosage, duration of action and effect are being carried on at our clinic and elsewhere.

MECHANICAL THERAPY

The "Vas-Oscillating Bed" (Sanders).—A form of mechanical treatment which has recently been used in a number of clinics is the motor bed described by Sanders.[47] By means of this bed the head and feet of the patient are alternately elevated and lowered, a complete cycle taking from one to three minutes. The movement is smooth; the patient soon becomes accustomed to it, and we have had patients on these beds for as long as two years. Most of them have continued its use during the sleeping hours long after their open lesions have healed. The degree of tilting and the speed of the cycle can be regulated within reasonable limits. The object is to exercise the arteries which are still able to function by producing rubor and pallor (engorgement and ischemia), as with the Buerger exercises, but continuously and without fatigue to the patient. This process is gentle, involves no constricting bands and appears theoretically sound, especially for the treatment of arteriosclerosis with or without gangrene. My associates and I use a thermostatically controlled cradle at 96 F. (35.7 C.) for adjunct treatment. While the total experience with this equipment has been rather limited, we have now had the opportunity to study about 50 cases. Clinical impressions are often deceptive guides, and experimental studies are not available, but so far the workers in our clinic and in other clinics [48] have been favorably impressed. Healing of ulcers has taken place in certain patients after complete failure of the pressure-suction boot and the reactive hyperemia machine. Many patients can use this equipment who are made very uncomfortable by the action of the boot or cuff. Thus far the condition indicating its use appears to be advanced

47. Sanders, C. E.: Cardiovascular and Peripheral Vascular Diseases: Treatment by a Motorized Oscillating Bed, J. A. M. A. **106**:916 (March 14) 1936.

48. Baker, N., and Roth, G.: Treatment of Occlusive Arterial Disease of Legs by Means of Saunders Vasocillator (Saunders Bed), Am. Heart J. **18**:312 (Sept.) 1939.

arteriosclerosis of the vessels of the legs with impending or actual early gangrene. The results in certain cases of such involvement have been encouraging in that the symptomatic progress of the condition has been checked and reversed, with improvement and healing. We should like to suggest a thorough study of the possibilities of this treatment for cerebral arteriosclerosis, for which to date there has been no treatment of sufficient value to be taken seriously.

Progress in this type of case is slow, and we find it usually necessary to keep the patient on the bed for at least one month. In our experience, treatments of a few hours' duration are not satisfactory. We have set a minimum in our clinic of eight hours a day. Use of the bed for patients with thromboangiitis obliterans seems rarely necessary, since the proper use of typhoid vaccine is satisfactory in most cases.

PRESSURE SUCTION BOOT

Although variations in environmental pressure have been used in the treatment of impaired circulation since before 1800, it remained for Landis and Gibbon [49] and Herrmann and Reid [50] to perfect suitable mechanical apparatus and to popularize this principle for widespread use in the treatment of peripheral vascular disease.

The principle on which the modern apparatus is established depends on the hypothesis that blood flow in an extremity can be increased appreciably by exposing the extremity to fluctuations in pressure from positive to negative and back to positive, continuing such alternations for the duration of the treatment, which may be from one to twenty-four hours or more. The extremity is contained in a so-called boot made of glass or metal in which the pressure changes are produced by means of connections to a correctly constructed air pump system. The opening through which the leg is inserted is made air tight by means of any of a number of types of rubber cuff. There have been certain disagreements as to the type and timing of the cycle to be used and the amounts of pressure and suction desirable. At present the most commonly used cycle approximates those suggested by Herrmann and is

49. Landis, E. M., and Gibbon, J. H., Jr.: The Effects of Alternating Suction and Pressure on Circulation in the Lower Extremities, Proc. Soc. Exper. Biol. & Med. **30**:593 (Feb.) 1933; The Effects of Alternate Suction and Pressure on Blood Flow to the Lower Extremities, J. Clin. Investigation **12**:925 (Sept.) 1933.

50. Herrmann, L. G.: Syphilitic Peripheral Vascular Diseases: Treatment by Means of an Intermittent Negative Pressure Environment, Am. J. Syph. **17**: 305 (July) 1933. Herrmann, L. G., and Reid, M. R.: The Pavaez (Passive Vascular Exercise) Treatment of Obliterative Arterial Diseases of the Extremities, J. Med. **14**:524 (Dec.) 1933. Herrmann, L. G.: Passive Vascular Exercises, Philadelphia, J. B. Lippincott Company, 1936.

as follows: With atmospheric pressure as the base line, one complete cycle takes fifteen seconds. The first three second period is one of positive pressure, reaching gradually 20 mm. of mercury. There is then a gradual downward curve, crossing the base line in the third second and proceeding to a negative pressure of —80 mm. of mercury at the eleventh second. A more rapid return to the base line completes the cycle in fifteen seconds. This is, of course, repeated continuously for the duration of each treatment.

Certain objections had to be met to make this treatment satisfactory theoretically and practically. In order to operate the boot the cuff around the upper part of the extremity must be air tight. This produces a certain degree of constriction about the limb and hence interferes with the blood flow, especially in the superficial vessels. Many types of cuff have been devised, and some have overcome this objection at least partially.

In general, when the circulation to an extremity is increased there is an increase in the surface temperature of that extremity. It has been noted in our clinic and elsewhere that the temperature of the limb is often colder after this type of treatment than before. This may be due to the aforementioned constriction or to the continuous flow of air in and out of the boot. As a result of that observation, local or reflex heat has been used, with improvement in this regard. The degree of dilatation depends on the potential capacity of the vessels, damaged and undamaged. As with all new or rediscovered methods of treatment, the first claims for this method represented a somewhat optimistic picture of its usefulness. It was stated that it was of great value for arteriosclerosis (senescent and diabetic), thromboangiitis obliterans, Raynaud's disease, acute embolism, frostbite and other forms of circulatory impairment. Actual experience with this apparatus has, in my opinion, greatly narrowed the indications for its use. At present I feel that it may be useful in selected cases of uncomplicated senescent or diabetic arteriosclerotic gangrene, acute embolism or thrombosis and frostbite. Even for certain of these conditions I must confess that I am not absolutely convinced as to its value. On the other hand, certain contraindications for its use have been definitely established.

Pressure suction should never be used in the presence of an acute or subacute infectious process or of any form of acute or subacute thrombophlebitis (which includes most forms of thromboangiitis obliterans) or in any case in which evidence of autolysis of the tissues is noted, such as a case of acute embolism or thrombosis (e. g., arteriosclerotic sudden occlusion) in which after several days the skin becomes mottled and blistered. In these conditions the results of its use may be serious. It appears futile to use it when the level of application of

the cuff is peripheral to the level of arterial blockage, yet this is being done constantly. Allen and Brown,[51] Conway[52] and Wilson and Roome[53] reported unsatisfactory results in the treatment of thromboangiitis obliterans, and even Reid and Herrmann[54] have recently stated that they were no longer so enthusiastic as to the ultimate results. My associates and I do not use it in the treatment of thromboangiitis obliterans, having observed more satisfactory results with typhoid vaccine.

Kountz[55] reported pressure suction to be of little value in experimental and clinical studies and devised an apparatus with a series of cuffs to be applied serially the length of an extremity, these to be operated in sequence and tending to "milk" the blood along the limb. Increasing the temperature up to 40 C. (104 F.) increased the flow about 8 per cent in normal but less in diseased extremities. Iontophoresis produced a similar response. Kountz and Smith[56] reported encouraging results with this equipment in 23 cases of arteriosclerosis and thromboangiitis obliterans. Their results are difficult to interpret, however, because in addition to this mechanized treatment (*a*) hypertonic saline solution was given intravenously twice a week, (*b*) alcohol was given daily by mouth and (*c*) patients with thromboangiitis obliterans received typhoid vaccine intravenously.

Further, more carefully controlled studies must be done to evaluate this type of equipment. I have had no personal experience with it.

REACTIVE HYPEREMIA AND INTERMITTENT VENOUS OCCLUSION

The phenomenon of "reactive hyperemia" has long been recognized. Among the early descriptions are those of Cohnheim[57] and Lister.[58]

51. Allen, E. V., and Brown, G. E.: Intermittent Pressure and Suction, J. A. M. A. **105**:2029 (Dec. 21) 1935.

52. Conway, J. H.: Obliterative Vascular Disease: Report of Fifty-One Cases Treated with Passive Vascular Exercise, J. A. M. A. **106**:1153 (April 4) 1936.

53. Wilson, H., and Roome, N. W.: Passive Vascular Exercise: Observations on Its Value in the Treatment of Peripheral Vascular Diseases, J. A. M. A. **106**:1885 (May 30) 1936.

54. Reid, M. R., and Herrmann, L. G.: Non-Operative Treatment of Peripheral Vascular Diseases, Ann. Surg. **102**:321 (Sept.) 1935.

55. Kountz, W. B.: Re-Establishment of the Circulation in Extremities, Arch. Phys. Therapy **20**:157 (March) 1939.

56. Kountz, W. B., and Smith, J. R.: Observations on Passive Vascular Exercise and Other Forms of Treatment of Peripheral Vascular Disease, Am. Heart J. **16**:55 (July) 1939.

57. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, A. Hirschwald, 1872.

58. Lister: Bull. Acad. de méd., Paris **8**:640, 1878; cited by Lewis and Grant.[60]

The superficial manifestation is a bright flush of the skin which occurs after release of a circulatory obstruction. Bier [59] studied this phenomenon for many years and developed therapeutic procedures based on the principle that obstruction and then release of the circulation would produce a marked circulatory increase and that this would be beneficial for certain pathologic states. This reflex was at first thought to result from vasomotor paralysis produced by pressure of the constricting band on the nerves, but Bier demonstrated that it can occur when every connection between the limb and the body has been severed except the artery itself. (This apparently does not, however, include severance of the sympathetic nerves of the arterial wall.) Lewis and Grant [60] showed that hyperemia of the skin occurs on restoration of the circulation even though the cutaneous nerves have degenerated. Anesthetic skin cannot be differentiated by its reaction from normal skin. The reaction appears to be independent not only of the central nervous system but of local nervous reflexes.

Bier [59] and Zak [61] expressed the opinion that when the circulation is occluded the venous blood stagnating in the vessels causes them to contract and that "reactive hyperemia," which follows release of the circulation, is a direct response of the vessels to the incoming blood.

Katzenstein [62] and Krogh [63] disagreed with this hypothesis, the latter especially taking exception to the theory that venous blood causes vessels to constrict while arterial blood causes them to dilate. Bier's conception depends on the supposition that the tone of the vessels is increased during occlusion and decreased when arterial blood enters them. Lewis and Grant have, however, presented evidence that this is not so and that dilatation of the vessels responsible for the cutaneous hyperemia occurs during the occlusion and not at the release.

The exact mechanism by which this takes place has been difficult to determine, involving, as it probably does, complex intracellular and extracellular chemical problems. As Roy and Brown [64] pointed out, it

59. Bier, A.: Hyperämie als Heilmittel, ed. 2, Leipzig, F. C. W. Vogel, 1905; Contributions to the Physiology and Pathology of Circulation, translated by J. B. Linn, New York, privately printed, 1905.

60. Lewis, T., and Grant, R.: Observation upon Reactive Hyperemia in Man, Heart **12**:73 (June) 1925.

61. Zak, E.: Ueber den Gefässkrampf bei intermittierenden Henken und über gewisse papillomotorische Erscheinungen, Wien. Arch. f. inn. Med. **2**:405 (June) 1921.

62. Katzenstein, M.: Ueber Entstehung und Wesen des arteriellen Collateralkreislaufs, Deutsche Ztschr. f. Chir. **77**:189, 1905.

63. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922.

64. Roy, C. S., and Brown, J. G.: The Blood-Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879; cited by Lewis and Grant.[60]

represents an attempt on the part of tissues deprived of a proper blood supply to become repossessed of it.

It should be emphasized that hyperemia represents a phenomenon which is constantly occurring. The part which bears the weight of the body necessarily becomes ischemic. When one moves about, shifting the weight, there is a flood of blood into the ischemic tissues to compensate for the accumulated debt to local metabolism. When the weight is too constantly on certain areas or when the vascular tree does not permit this compensation, necrosis occurs. Lewis and Grant [60] published instructive studies of this phenomenon as it occurs after both arterial and venous obstruction and release. Recent interest in the subject warrants a brief review of certain of their pertinent observations. In relation to *arterial* reactive hyperemia these authors reached the following conclusions.

1. Increase in the environmental temperature within certain limits produces a definite increase in the response; e. g., with temperatures of 15 to 20 C. the increase in flow on release of the constriction was 2 cc. in 600 cc. of tissue, whereas at a temperature of 40 C. an identical plethysmographic experiment produced an increase of 15 to 20 cc. of blood flow per minute to 600 cc. of tissue. It is thus very important that in all such studies the temperature should be carefully controlled.

2. Within certain limits, the longer the duration of occlusion the greater is the duration of the subsequent hyperemia. The flush usually lasts approximately one-half to three-quarters as long as the preceding occlusion. Occlusion lasting more than twenty minutes is very uncomfortable, and if it lasts for hours it may produce paralysis,[65] thrombosis or other serious effects.

3. If a series of plethysmographic curves is taken in which the periods of occlusion are constant and equal to the intervening intervals, the individual curves are identical in form. (Only five successive curves were reported.)

4. Arterial reactive hyperemia following an occlusion lasting ten minutes produces a greater effect than soaking the arm in water at 43 to 44 C. for thirty minutes. (As has been pointed out in this article, direct heat does not produce as great an increase in blood flow as does reflex heat.[19])

5. Exercise, according to comparative studies, produces an increase in blood flow which is greater in volume and duration than that pro-

65. von Volkmann, R., in Pitha, F. J., and Billroth, T.: Handbuch der allgemeinen und speciellen Chirurgie, Stuttgart, Ferdinand Enke, 1882, vol. 2, pt. 2 A, p. 846.

duced by reactive hyperemia. In reactive hyperemia all the soft tissues seem to be affected, while in exercise the effect is mostly confined to the muscles.

In relation to *venous* reactive hyperemia the authors concluded:

1. When occlusion of the venous return flow is produced, the venous pressure, within certain limits and with slight variations, rises to equal the cuff pressure.

2. When the pressure is 40 to 50 mm. of mercury for two minutes or more the pulse volume begins to increase; this becomes maximal in ten to fifteen minutes.

3. When a pressure of 20 to 30 mm. of mercury in the cuff is released the plethysmographic curve is that of a simple drop to the base line as the veins empty themselves.

4. If the cuff pressure has been higher (40 to 60 mm. of mercury) the descent of the curve is broken by a hesitation, or a secondary "hump" and reactive hyperemia occurs.

5. The size of this "hump," within certain limits, is increased by (*a*) increasing the cuff pressure, (*b*) maintaining the cuff pressure for longer periods and (*c*) raising the temperature.

6. This "hump" is in all probability produced by superimposed arterial active dilation and filling to a point at which the arterial blood is entering the limb more rapidly than the veins are emptying.

7. Obliteration of the major artery supplying the limb will obliterate the hump.

8. Venous congestion carried to a high point (a pressure of 70 mm. of mercury) for five to ten minutes seems to yield a curve of vasodilatation not dissimilar in amplitude and duration to that produced by a somewhat shorter period of arterial occlusion.

9. The release of venous congestion in a normal limb is followed by flush displacing the cyanosis and varying in duration with the degree and duration of the previous congestion.

"The phenomenon of reactive hyperemia is related in its degree to one factor—namely, to the blood flow debt which is usually a product of the amount by which flow is reduced and the time over which the reduction has been maintained."

The hyperemia results from active dilation of those vessels which are responsible for the color of the skin, namely the arterioles, capillaries and venules. As has been stated, the mechanism is extremely complex; the nervous reaction theory appears untenable. Other factors, including oxygen deficiency and accumulation of carbon dioxide or of other metabolites, such as pituitary hormones, have been studied, without conclusive results.

The problem of possible therapeutic application of these principles has been emphasized by Bier and more recently by Collens and Wilensky,[66] who have developed an "intermittent venous hyperemia machine" which is capable of reproducing a cycle with the pressure and timing believed desirable.

Several questions must be considered carefully in this regard. Since the phenomenon of reactive hyperemia depends on and is related directly to a preceding "blood flow debt" accumulated during the period of occlusion, is it beneficial or dangerous to tissues which are barely receiving enough nourishment for life to go through periods of increased nutritional debt, even though the hyperemia may compensate later?

If the response of normal persons to arterial reactive hyperemia is much more satisfactory than that to venous reactive hyperemia, should not production of the former be theoretically the technic of choice?

What is the relation of the experiment of Lewis and Grant (in which, by pressure occlusion of the subclavian artery the reactive venous hyperemia was abolished) to arterial obliterative vascular disease and this type of therapy? After repetition of this phenomenon a great many times, does a fatigue syndrome set in, affecting the reaction?

These and many other questions must be answered before the theoretic conclusions are accepted as satisfactory. Veal and McCord [67] have studied the effects of complete arterial occlusion and intermittent venous occlusion on the oxygen content of the blood with the following results: After complete arterial occlusion of the arm for five to eight minutes followed by release, the oxygen saturation of the blood from the antecubital vein showed a definite rise in one minute in 9 of 11 cases. The saturation then decreased at varying rates. After intermittent venous occlusion, however, the tendency was reversed. In 8 of 11 cases there was a definite decrease in oxygen saturation of the blood at the end of one minute after release of the compression. There was no significant change at the end of three minutes. This raises the question whether by "using the cycle 2:2 or 2:1 minutes" and the compression recommended (25 to 80 mm. of mercury) true reactive hyperemia is produced. Perhaps the fatigue phenomenon previously mentioned

66. Collens, W. S., and Wilensky, N. D.: (*a*) The Treatment of Peripheral Obliterative Arterial Diseases by the Use of Intermittent Venous Occlusion, J. A. M. A. **107**:1960 (Dec. 12) 1938; (*b*) Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, Am. Heart J. **11**:705 (June) 1936; (*c*) An Apparatus for the Production of Intermittent Venous Occlusion, ibid. **11**:721 (June) 1936; (*d*) Peripheral Vascular Diseases, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

67. Veal, J. R., and McCord, W. M.: Blood Oxygen Changes Following Intermittent Venous Occlusion, Am. Heart J. **17**:401 (April) 1939.

entered into these studies. This possibility is not mentioned. Allen and McKechnie [68] studied the effect of intermittent venous occlusion on the cutaneous temperature under controlled conditions. In 19 patients (9 normal subjects and 10 persons with hypertension, arthritis and peripheral vascular disease) they found no evidence that any significant or consistent vasodilatation resulted from the procedure.

Clinical evaluation of either Bier's hyperemia or intermittent venous hyperemia is extremely difficult. It appears that Bier's hyperemia has been largely abandoned in the United States, either because of lack of conclusive therapeutic results or because new methods seem to offer greater promise. I have never been impressed with the clinical results of this technic in the treatment of arteriosclerosis obliterans or thromboangiitis obliterans and have long since ceased to use it.

The status of intermittent venous hyperemia must, in all fairness, be considered as not definitely established. Collens and Wilensky have repeatedly reported excellent results as following its use, but many of their patients were also treated with a regular "vascular regimen" involving abstinence from smoking, warmth and rest (in certain cases), and these factors confuse the picture somewhat. de Takáts, Hick and Coulter [69] reported favorably on the use of this technic in a series of 10 cases, but their conclusions were weakened by the fact that other treatments were used simultaneously, and their series was too small to permit the drawing of any positive conclusions.

Kramer,[70] Brown and Arnott [71] and Wilson and Ogston [72] have also reported favorably on this technic.

In the vascular disease clinic and in the wards of the New York Post-Graduate Medical School and Hospital we studied and used this apparatus in 23 cases over a period of about one year. Occlusive conditions of varying severity were used—some advanced and severe, with gangrene; others early and less severe, without gangrene. In

68. Allen, E. V., and McKechnie, R. E., Jr.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities: Studies of Skin Temperature, J. Lab. & Clin. Med. **22**:1260 (Sept.) 1937.

69. de Takáts, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, J. A. M. A. **108**: 1951 (June 5) 1937.

70. Kramer, D. W.: Periodic or Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, M. Rec. **147**:99 (Feb. 2) 1938.

71. Brown, J. J. M., and Arnott, W. M.: Intermittent Venous Occlusion in the Treatment of Obliterative Vascular Disease, Brit. M. J. **1**:1106 (May 29) 1937; Treatment of Obliterative Vascular Disease by Intermittent Venous Occlusion: Further Observations, ibid. **1**:616 (March 19) 1938.

72. Wilson, C., and Ogston, A. G.: Treatment of Peripheral Vascular Disease by Intermittent Venous Occlusion: New, Simple and Inexpensive Method, Lancet **1**:606 (March 12) 1938.

some instances the cuff was active on the patient practically continuously for as long as six weeks, so that it cannot be charged that it was not given a satisfactory opportunity to demonstrate its worth. We are perfectly willing to admit the difficulty of attempting to evaluate the effects of any therapy on the course of such conditions, but the members of our clinic were unconvinced of the value of the method, and in some instances it was felt to have been harmful. It was therefore discontinued as a routine measure.

Certain contraindications for its use became apparent: (1) a level of arterial blockage above the level of the cuff; (2) active and spreading infection of the wound, especially with streptococci or anaerobic bacteria; (3) extreme toxicity of the patient, and (4) increased pain with the use of the machine. (Collens and Wilensky suggested using a 25 mm. pressure in certain cases. Lewis and Grant have shown that reactive venous hyperemia probably does not occur to any appreciable amount at this pressure.)

For most cases a compression of 60 mm. of mercury and a cycle of two minutes "on" and two minutes "off" is optimal. The treatment may last from one hour to several months if the patient tolerates it well. Reflex heat, as previously described, is advisable but I do not advise the use of short wave therapy or diathermy for the involved foot as suggested by Collens and Wilensky.[60d]

This treatment appears indicated largely for arteriosclerosis obliterans and to a lesser degree for thromboangiitis obliterans, but the cases must be carefully selected.

COMMENT AND SUMMARY

An attempt has been made to review and evaluate the more important of the methods used in conservative treatment of occlusive peripheral vascular disease, especially arteriosclerosis obliterans and thromboangiitis obliterans. The more general use of the conservative approach definitely affects the statistics on amputations. It should be recognized that it is far better surgery to take meticulous care of small lesions and produce healing than to perform major amputations. In a series of 100 consecutive cases of thromboangiitis obliterans [73] studied since 1931 by Littauer and me only 3 major amputations were performed, all on persons who would not stop smoking. Most of the patients have been followed for two to eight years. The incidence of amputation in this group may be expected to rise with the trauma and other factors incident to the passage of time, but it is extremely doubtful

73. Wright, I. S., and Littauer, D.: An Analysis of the Results of Conservative Therapy in One Hundred Cases of Thrombo-Angiitis Obliterans, to be published.

that the former amputation rate of 40 to 50 per cent will again be observed. For arteriosclerosis obliterans our figures are not so encouraging. We have not yet compiled statistics on this condition, but we have been impressed by its more hesitant response to therapy. On the other hand, an increasing number of patients who have been advised to submit to amputation are today walking on the condemned leg as a result of conservative therapy. Continued study may result in greater success in this regard. Amputation must be regarded as an admission of defeat, an acknowledgment of the physician's inability to solve the problem with which he is confronted.

It is important that the recent trend in certain quarters toward submitting all patients with vascular disease to the same form of therapy, whether it be use of the pressure suction boot, administration of hypertonic saline solution or intravenous administration of typhoid vaccine, be discouraged. The problems presented by different diseases and by different patients with the same disease are more frequently unlike than identical. Each should be given individual consideration before the therapeutic regimen is instituted. It is also of vital importance that the conception that peripheral vascular disease is purely local, involving only the extremities, be overcome. Each patient should be submitted to a complete study in order that evidences of vascular damage anywhere in the body may be discovered and proper therapy instituted. For example, it is not yet generally recognized that thromboangiitis obliterans may affect any artery in the body.

This whole field is just beginning to "open up." New studies are constantly being reported which modify the current conceptions. I am deeply conscious of the limitations of such a review as this. Another decade will no doubt clarify many of the issues raised in this symposium.

THROMBOANGIITIS OBLITERANS

TREATMENT WITH SODIUM TETRATHIONATE AND SODIUM THIOSULFATE

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AND
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Thromboangiitis obliterans is a clinical and pathologic entity characterized by peripheral arterial thromboses of obscure origin.[1] On the basis of our investigative work, we have concluded that thromboangiitis obliterans in the majority of our cases is associated with the following factors: (*1*) changes in the blood; (*2*) disturbed tissue metabolism; (*3*) arterial and venous thromboses, which occur most frequently in the peripheral vessels but may occur in any part of the body, and (*4*) local infection in the involved extremity. Until the complex adjustments which compensate for pathologic conditions of the blood are better understood, it will be difficult to detect the disease before serious circulatory deficiency results from arterial thrombosis. Infection, infarcts or gangrene frequently directs attention to the circulatory disease.

Various changes in the blood have been reported since Koga[2] first, in 1913, reported increased viscosity. In cases of acute involvement we have reported increased viscosity of the blood, rapid sedimentation of the cells, rapid coagulation, increased alkalinity and arterial-like oxygen saturation of the superficial venous blood from the involved extremity.[3] In improved or recovered patients with thromboangiitis obliterans and in patients with other peripheral circulatory diseases these conditions

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1. (*a*) Homans, J.: A Text Book of Surgery, Springfield, Ill., Charles C. Thomas, Publisher, 1931. (*b*) Buerger, L.: Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

2. Koga, G.: Treatment of Spontaneous Gangrene of the Extremities, Deutsche Ztschr. f. Chir. **121**:371-382 (Feb.) 1913.

3. Theis, F. V., and Freeland, M. R.: The Blood in Thrombo-Angiitis Obliterans, Arch. Surg. **38**:191-205 (Feb.) 1939.

of the blood were not present. These findings indicated that there is a relation between the stage of the disease and the complex factors of the pathologic physiology of the blood. To evaluate the importance of changes in the blood, observations should be made while thromboses are forming and during the acute stage of the disease.

Our study of the blood in thromboangiitis obliterans included an investigation of the changes produced by smoking. We reported [4] that smoking by patients with thromboangiitis obliterans generally results in decreased peripheral cutaneous temperatures, increased pulse rate, elevated blood pressure, decreased oxygen saturation of the arterial blood, decreased oxygen saturation of the venous blood in patients with acute thromboangiitis obliterans and increased oxygen saturation in the improved patients and in normal controls. Most of the responses seem to be physiologic protective adjustments to reduced oxygen saturation of the arterial blood. Failure of compensatory adjustment to heavy smoking in some persons may be a cause of thromboangiitis obliterans leading to thrombosis.

Maddock and Coller [5] reported that nicotine is the important ingredient of tobacco and that the deleterious effect of smoking is due to the pharmacologic action of nicotine on the peripheral sympathetic nerves. On the contrary, we found that the specific action of smoking is not entirely on the sympathetic nerves. We observed a decline in temperature of 4 degrees (C.) on the sympathectomized fingers after smoking in a case of Raynaud's disease. Similar response to epinephrine was observed on sympathectomized extremities in cases of Raynaud's disease by Smithwick, Freeman and White.[6] These observations suggest that the effect of smoking on the pulse, blood pressure and peripheral temperatures is due to substances in the circulating blood in addition to sympathetic vasomotor stimulation of the peripheral vessels.

In the treatment of thromboangiitis obliterans we have had considerable clinical success with sodium tetrathionate ($Na_2S_4O_6 \cdot H_2O$) [7] and sodium thiosulfate ($Na_2S_2O_3 \cdot 5\ H_2O$). This treatment was directed

4. Theis, F. V., and Freeland, M. R.: Smoking and Thrombo-Angiitis Obliterans, Ann. Surg., to be published.

5. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, Ann. Surg. **98**:70-81 (July) 1933.

6. Smithwick, R. H.; Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause of Failure of Operation for Raynaud's Disease, Arch. Surg. **29**:759-767 (Nov.) 1934.

7. Sodium tetrathionate has been prepared for us experimentally and supplied by G. D. Searle and Company, of Chicago.

toward improvement of the condition of the blood. The following facts seem pertinent: 1. Pathologic changes in the blood are present during the acute stage of the disease. 2. Clinically, smoking is associated with an acute attack of the disease, and we believe that heavy smoking may contribute to the changes in the blood. 3. Sodium tetrathionate and sodium thiosulfate are of clinical value in the treatment of the disease. We are reporting the results of our investigation of the effect of these solutions on various changes in the blood and physiologic responses which are affected by smoking. The two solutions are referred to as the inorganic sulfur compounds.

Fig. 1.—Patient with thromboangiitis obliterans. The blood picture in his case is given in table 2. The left leg was amputated in 1935. There was recurrence of the disease in the right foot in 1936.

METHOD OF INVESTIGATION

The methods of obtaining peripheral temperatures, pulse rate and blood pressure and of collecting and analyzing the blood were the same as those used in our previous work.[8] Determinations of glutathione were made by the method of Woodward and Fry.[9]

8. Theis, F. V., and Freeland, M. R.: Peripheral Circulatory Disease: Effect of Alternating Positive and Negative Pressure Treatments on Venous Blood and the Skin Temperatures, J. A. M. A. **197**:1097-1104 (Oct. 7) 1936; footnotes 3 and 4.

9. Woodward, G. E., and Fry, E. G.: The Determination of Blood Glutathione, J. Biol. Chem. **97**:465-482 (Aug.) 1932.

After the period of stabilization of the subject at rest in bed and initial observation of peripheral temperatures, pulse rate and blood pressure, specimens of arterial blood from the right radial artery or of venous blood from the right antecubital vein were obtained under oil and immediately transferred to mercury tonometers. Injections of sodium tetrathionate or sodium thiosulfate in 10 cc. of triple-distilled water were given in the left antecubital vein, and ten minutes later specimens of blood were again withdrawn from the right side. The various observations mentioned were repeated under the same resting conditions after the injection.

RESULTS

Peripheral Temperatures.—The average temperature of the fingers and toes was usually increased after intravenous injection of either solution. Figure 2 shows that the inorganic sulfur compounds had

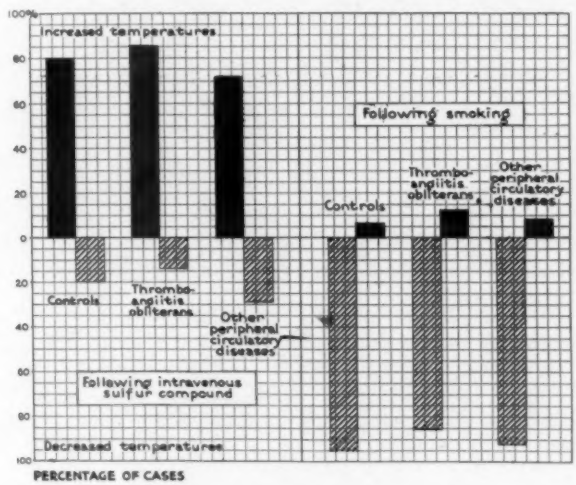

Fig. 2.—Changes in peripheral temperature of the skin. The inorganic sulfur compounds produced the opposite effect on the temperatures to that which occurred after smoking. Increased temperature is indicated by solid black; decreased temperature, by diagonal lines.

an action that was the opposite of smoking. The more rapid and higher elevations in temperatures were produced by the sodium thiosulfate solution, but the effect was of shorter duration than with sodium tetrathionate. Decreased temperatures were occasionally observed, especially in nervous patients, probably as a result of the puncture.

Cutaneous temperatures were more constantly increased when no element of vasoconstriction was present. In completely sympathectomized extremities or when block of the peripheral nerves with procaine hydrochloride had demonstrated organic circulatory disease, the inorganic sulfur compounds still produced an increase in cutaneous temperature of 0.5 to 1 degree (C.). Since vasomotor action was no

longer present in these cases, the increased cutaneous temperatures were produced through the blood stream, probably as a result of increased local tissue metabolism.

Blood Pressure.—The extent of the reduction in blood pressure which frequently followed injection of inorganic sulfur compounds in patients with thromboangiitis obliterans depended on the initial pressure. High initial levels responded with a greater reduction in pressure. In the acute stage of the disease the blood pressure was not elevated; consequently a less marked reduction occurred after injection. The reduction varied from 8 to 40 mm. of mercury in different patients and also in the same patient on different days. The diastolic pressure was less affected than was the systolic, although the two were occasionally affected to the same extent.

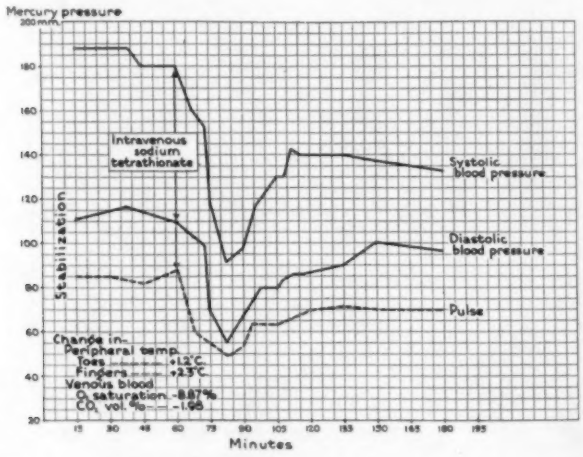

Fig. 3.—Effect of inorganic sulfur on a patient with essential hypertension and peripheral circulatory symptoms. Marked symptomatic relief accompanied reduction in the systolic and diastolic blood pressures and in the pulse rate after intravenous injections of 0.4 Gm. of sodium tetrathionate. Bimonthly and then monthly injections over a period of eighteen months have maintained the subjective and objective improvement.

Hypertension with peripheral circulatory symptoms (fig. 3) may be benefited by intravenous injections of the sulfur compounds to the same degree as the circulatory diseases with hypertension, especially when smoking is a cause of the elevated pressure (fig. 4). The immediate reduction in pressure which followed injection was almost always transitory, but occasionally with subsequent injections the pressure remained at a lower level. Sodium tetrathionate produced a more constant and longer-lasting effect in lowering the pressure than did sodium thiosulfate.

Pulse Rate.—The pulse rate was usually slower after injection of the solutions, especially when the initial rate was higher than normal. With a rate of 80 or 90 per minute, a drop to 70 or less was not uncom-

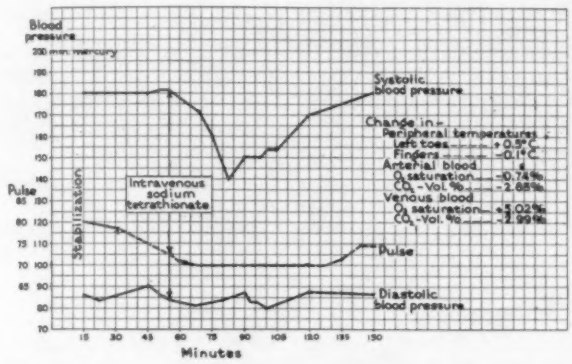

Fig. 4.—Effect of inorganic sulfur on a clinically well patient with thromboangiitis obliterans and hypertension who continued to smoke two or more packages of cigarets daily. The right leg had been amputated. In addition to the marked reduction in blood pressure and slowing of the pulse rate, insignificant changes occurred in the peripheral temperatures and in the arterial oxygenation after injection of 0.6 Gm. of sodium tetrathionate. Clinical improvement has been maintained for four years by biweekly injections, despite heavy smoking.

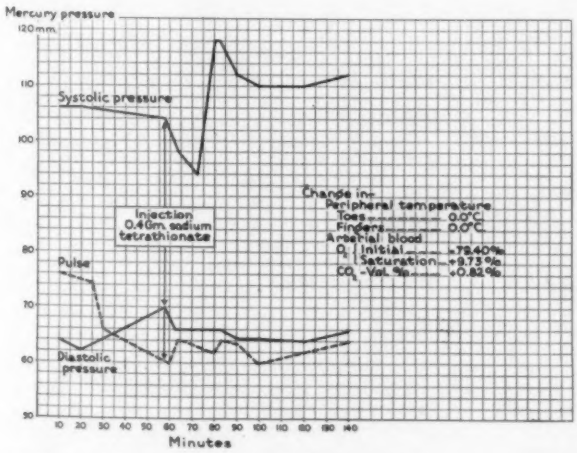

Fig. 5.—Effect of inorganic sulfur on a patient with Raynaud's disease. The initial oxygen saturation of the arterial blood was 79.40 per cent. Normally, in this vicinity the oxygen saturation is from 92 to 95 per cent. After injection of 0.4 Gm. of sodium tetrathionate, elevation of the initial low blood pressure was accompanied by an increase of 9.73 per cent in oxygen saturation of the arterial blood and by a reduction in the pulse rate.

mon. The effect of the inorganic sulfur compounds on the pulse rate was of longer duration than its effect on the blood pressure.

In 2 cases of Raynaud's disease with initial low oxygenation of the arterial blood and low blood pressure, injection of the tetrathionate solution was followed by elevation of the blood pressure to a normal level, slowing of the pulse and increased oxygen saturation of the arterial

TABLE 1.—*Changes in the Oxygen and Carbon Dioxide Content of the Arterial Blood and in the Peripheral Cutaneous Temperatures Ten Minutes After Intravenous Injection of an Inorganic Sulfur Compound*

	Oxygen Capacity, Vols. %	Initial Oxygen Saturation, %	Change in Oxygen Saturation, %	Change in Carbon Dioxide, Vols. %	Change in Temperature	
					Toes	Fingers
Controls (normal)						
Average for 10 patients....	20.24	93.20				
Mr. A.....	20.96	93.91	—2.09	—1.34	—0.9°C.*	—0.5°C.*
Mr. K.....	18.20	94.40	+1.90	—5.40	—0.3°C.*	—0.7°C.*
Peripheral circulatory disease (thromboangiitis obliterans)						
Mr. P.....	19.16	87.50	+3.85	+0.62	—0.4°C.	+1.5°C.
Mr. S.....	16.86	91.89	+2.25	—2.13	+0.2°C.	+0.2°C.
Mr. K. 7/27/39.....	11.00	96.10	—8.70	—1.50	+1.3°C.	+0.4°C.
8/10/39.....	17.60	96.10	—5.80	—0.80	.....	.....
Mr. Z.....	11.68	94.00	.....	.....	.....	.....
Mr. B., 6/17/37.....	20.48	88.14	+1.05	—2.10	+0.4°C.	+1.3°C.
6/23/37.....	19.65	93.44	—3.24	—1.85	+1.0°C.	+0.6°C.
Mr. S., 7/ 8/37.....	19.95	87.80	+1.30	—0.02	.....	.....
11/29/37.....	17.74	88.20	+0.80	—0.88	+0.2°C.	—0.2°C.
Mr. H.....	19.98	80.34	+3.82	—1.86	—1.2°C.	.....
Mr. P.....	17.71	94.82	—0.74	—2.83	+0.5°C.	.....
Mr. M.....	16.30	91.22	—1.58	—1.54	+0.5°C.	+0.2°C.
Mr. B., 4/19/39.....	14.29	81.20	.....	.....	.....	.....
7/22/39.....	20.00	91.40	+2.80	+0.05	+1.4°C.	+0.6°C.
Raynaud's disease						
Miss J., 2/9/39.....	16.64	79.40	+9.73	+0.82	0.0°C.*	0.0°C.*
6/8/39.....	16.68	93.00	+0.30	—0.20	0.0°C.	0.0°C.
Miss P.....	17.36	82.90	+14.00	+1.51	0.0°C.	—0.5°C.
Miss B.....	17.04	95.50	+0.30	—0.59	0.0°C.	+2.0°C.
Mrs. W.....	16.80	84.60	+6.50	.....	—0.9°C.	+3.2°C.
Senile arteriosclerosis						
Mr. T.....	15.75	98.65	—4.91	—0.70	+3.7°C.	+0.2°C.
Mr. R.....	.....	91.64	+0.32	.....	—2.5°C.	—0.3°C.
Unclassified conditions						
Mr. De.....	14.72	89.39	+2.29	—1.05	+0.6°C.	—1.2°C.
Mr. S.....	19.00	95.04	—2.21	+0.96	+3.5°C.	+0.8°C.
Mr. D.....	18.80	88.60	+4.90	+0.90	.....	.....
Mr. S.....	20.00	83.90	+14.80	.....	—0.9°C.	0.0°C.

* Decreased peripheral temperatures usually occurred in nervous patients when difficulty was encountered in performing arteriopuncture.

blood (fig. 5). This indicates a relation between the physiologic mechanism of blood pressure, the pulse rate and the oxygenation of the arterial blood.

Arterial Blood.—The oxygen capacity of normal arterial blood is from 19 to 21 volumes per cent in males and from 17 to 19 volumes per cent in females. In patients with thromboangiitis obliterans the capacity varied from 11 to 20 volumes per cent (table 1). Two patients had an oxygen capacity of only 11 volumes per cent without a reduc-

tion in the erythrocyte count and the hemoglobin index to account for the low capacity. The venous blood of another patient (no arterial blood obtained) had an oxygen capacity of 10 volumes per cent (table 2).

TABLE 2.—*Effect of Sodium Thiosulfate or Sodium Tetrathionate on Blood Withdrawn from the Right Cubital Vein Ten Minutes After Injection in Left Cubital Vein in a Case of Thromboangiitis Obliterans* *

	Oxygen Capacity, Vols.%	Content of: Oxygen, Vols.%	Content of: Carbon Dioxide, Vols.%	Oxygen Saturation, %	Percentage of Hemoglobin and Blood Counts per Cu.Mm.	Changes in Temperature: Toes	Changes in Temperature: Fingers
6/29/36: sodium thiosulfate, 2 Gm.; new case; no previous treatment							
Before injection	10.31	7.61	45.58	73.82	Hb. 78		
After injection	17.42	17.13	39.31	98.40	R.B.C. 4,080,000		
Change	+7.11	+9.52	—6.27	+24.58	W.B.C. 8,900	.....	.....
7/2/36: three days of sodium thiosulfate (2 Gm.)							
Before injection	10.08	6.81	52.02	67.60	Hb. 70		
After injection	14.70	12.30	45.57	83.67	R.B.C. 3,950,000		
Change	+4.62	+5.49	—6.45	+16.07	W.B.C. 9,900	.....	.....
12/10/36: no treatment for 5 months; improved but still has continuous rest pains							
Before injection (arm)	14.11	9.42	36.82	66.77	R.B.C. 4,100,000		
10 min. later (repeat)	.....	9.28	46.87	65.76			
After injection	13.32	10.50	45.06	78.80	R.B.C. 3,680,000		
Change	—0.79	+1.08	—1.76	+12.03		.....	+0.4
Before injection (leg)	15.22	5.13	47.02	33.70	R.B.C. 3,970,000		
After injection	14.28	6.05	49.27	42.38	R.B.C. 3,550,000		
Change	—1.06	+0.93	+2.25	+8.58		.....	—0.8
Coagulation time, 1¾ min. Sedimentation time, 16 min.							
12/23/36: two weeks daily treatment; sodium thiosulfate, 2 Gm. daily							
Before injection	15.10	12.02	39.55	79.60	R.B.C. 3,570,000		
After injection	15.17	12.08	39.10	79.60	R.B.C. 3,770,000		
Change	+0.07	+0.06	—0.40	0.00		+0.1	+0.8
1/6/37: sodium thiosulfate, 2 Gm. daily; marked clinical improvement; no pain							
Before injection	15.27	8.18	51.37	53.60			
After injection	15.25	10.46	47.88	68.60			
Change	—0.02	+2.28	—3.49	+15.00		+0.3	+1.3
4/1/37: improving; no treatment for four months							
Before injection	16.62	9.01	48.81	54.02	R.B.C. 4,070,000		
After injection	16.62	9.75	46.02	58.65	R.B.C. 4,800,000		
Change	0.00	+0.74	—2.79	+4.63		+0.8	+1.0
p_H before, 7.495 p_H after, 7.548							
1/13/38: injection of 0.6 Gm. sodium tetrathionate; no pain; improving; no treatment since April 1, 1937							
Before injection (arm)	15.78	12.08	37.64	76.54	R.B.C. 3,930,000		
After injection	15.59	8.80	38.02	56.43	R.B.C. 4,110,000		
Change	—0.19	—3.28	+0.38	—20.11		—0.9	+0.5
Before injection (leg)	15.02	4.62	41.50	30.77	R.B.C. 3,160,000		
Sedimentation time, 15 min.							

* There was an acute recurrence of the condition in the left foot. The right leg had been amputated (fig. 1).

The exceptionally low oxygen capacity in such patients may be due to some unknown ingredient of the dark blood which interferes with the analytic reagents or to some inactive form of hemoglobin. Spectroscopic and quantitative chemical tests have not revealed the presence of significant amounts of methemoglobin and carboxyhemoglobin.[3]

The oxygen saturation of normal arterial blood in this locality is from 92 to 95 per cent. In cases of thromboangiitis obliterans as well as of Raynaud's disease the oxygen saturation was found to be as low as 80 per cent. In cases with unusually low oxygen capacity, normal oxygen saturation was noted. Low blood pressure, especially in the presence of Raynaud's disease, may contribute to the low oxygen saturation of the arterial blood.

Treatment in these cases with sodium tetrathionate or sodium thiosulfate was usually followed by return of more nearly normal oxygen

TABLE 3.—*Changes in Oxygen Saturation of the Venous Blood After Injection of an Inorganic Sulfur Compound*

		Percentage of Oxygen Saturation							
		Increase				Decrease			
	No. of Patients Examined	No. of Tests	Maximum	Minimum	Average	No. of Tests	Maximum	Minimum	Average
Normal controls	11	2	9.46	3.26	6.36	9	15.27	0.5	5.5
Patients with peripheral circulatory disease									
Thromboangiitis obliterans	20	38	34.10	0.02	9.44	10	21.76	0.6	9.08
Neurocirculatory disease	7	4	32.94	6.2	14.18	5	6.34	1.26	3.94
Patients with polycythaemia vera (not thromboangiitis obliterans)	2	2	10.4	3.9	7.10	0	.....	....	....
Patients with arteriosclerosis									
Senile	2	2	5.4	1.8	3.6	0	.....	....	....
Diabetic	1	0	.....	....	....	1	19.75	....	....
Patients with frostbite	1	0	.....	....	....	1	6.3	....	....
Patients with thrombophlebitis									
Acute	1	1	2.1	....	....	0	.....	....	....
Recovered	2	0	.....	....	....	2	9.81	5.17	7.49

capacity, saturation of the arterial blood, blood pressure and pulse rate. Clinical improvement accompanied these changes.

Venous Blood.—After injection of the inorganic sulfur compounds the oxygen saturation of the venous blood was decreased in 81 per cent of the normal controls and increased in 79 per cent of patients with thromboangiitis obliterans (table 3). A similar increase in oxygen saturation occurred in 2 cases of Raynaud's disease. The fact that the change in oxygen saturation of the venous blood of patients with thromboangiitis obliterans was opposite to that which occurred in the normal controls is significant. The increased peripheral temperatures and the accompanying changes in the venous blood were the reverse of those which occurred after smoking (figs. 2 and 6).

The oxygen capacity of the venous blood of some patients (table 2) with thromboangiitis obliterans was increased after injection of the inorganic sulfur compounds. This has been discussed in connection with the arterial blood and was not due to changes in the erythrocyte counts and hemoglobin content. Since colorimetric hemoglobin standards are based on oxygen capacity, the aforementioned changes in the oxygen capacity of the dark arterial and the venous blood suggested activation of some inactive hemoglobin by the sulfur compounds.[10] An increase in glutathione, which is a sulfur-containing oxidation catalyst, may contribute to this action. The catalyst may be deficient in any of the body tissues, but its deficiency in the blood would be reflected throughout the body.

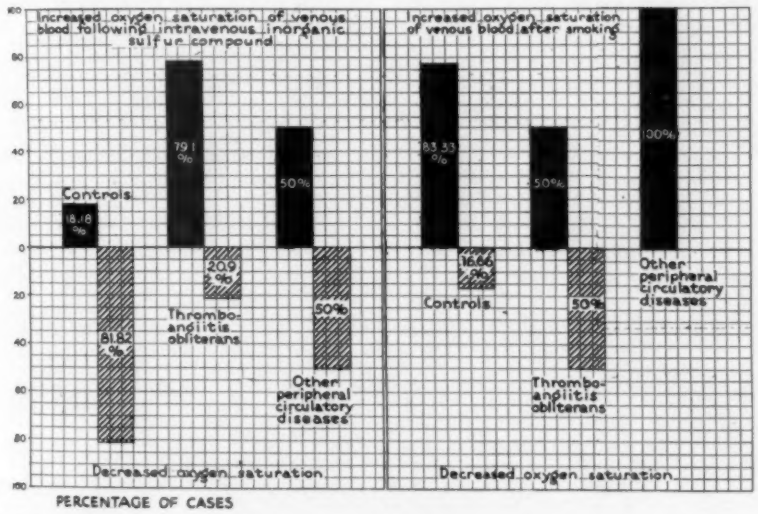

Fig. 6.—Changes in oxygen saturation of the venous blood from the right antecubital vein. Note the opposite effect of the inorganic sulfur to that of smoking.

Glutathione.—The utilization of oxygen by the tissues has been shown to be partly under the control of an oxidation catalyst, glutathione. This substance is found in the blood in two forms, the reduced, active form and the oxidized, inactive form. The results of our study of the glutathione content of the venous blood are contained in table 4. The average content for the normal controls and for patients with arteriosclerotic disease was practically the same.

10. Ammundsen, E.: The Presence of Non-Oxygen-Combining (Inactive) Hemoglobin in the Blood of Normal Individuals, Science **90**:372-373 (Oct. 20) 1939.

In 2 cases of acute thromboangiitis obliterans we found an unusually low content of the reduced form of the catalyst and a high content of the oxidized form. After intensive treatment with the inorganic sulfur

TABLE 4.—*Glutathione Content of the Venous Blood: Effect of Sodium Tetrathionate and Sodium Thiosulfate on Untreated and Treated Thromboangiitis Obliterans and Other Peripheral Circulatory Diseases*

	No. of Patients	No. of Tests	Glutathione, Mg./100 Cc. Total	Reduced	Oxidized	Comment
Controls						
Maximum	..	..	69.0	44.6	34.4	
Minimum	..	..	39.4	25.5	13.9	
Average	8	10	58.23	38.28	21.04	Normal
Peripheral Circulatory Diseases						
Thromboangiitis obliterans						
Acute						
Mr. E. New case; no gangrene or infection						
8/25			69.5	12.7	56.8	No treatment
8/27 Injection of 0.6 Gm. sodium tetrathionate						
Before injection			61.4	11.7	49.7	
After injection			61.3	12.7	48.6	
9/24 Injection of 1 Gm. sodium thiosulfate						
Before injection			83.8	52.6	31.2	Treated 4 weeks;
After injection			79.8	56.6	23.2	improved
Mr. M. Both legs involved previously; hands involved now						
8/30 Injection of 0.6 Gm. sodium tetrathionate						Recurrence
Before injection			61.4	18.1	43.3	
After injection			47.5	17.0	30.5	
9/10 Injection of 1 Gm. sodium thiosulfate						
Before injection			61.3	56.0	5.3	Intensive treatment
After injection			71.4	54.1	17.3	
Mr. S.						
9/9 Injection of 0.4 Gm. sodium tetrathionate						Intensive treatment
Before injection			61.30	38.28	23.02	two months;
After injection			61.40	38.20	23.20	improved
11/15 Injection of 1 Gm. sodium thiosulfate						Serious infection
Before injection			53.8	30.8	23.0	developed on calf
After injection			52.4	36.8	15.6	of leg
11/26 Injection of 0.6 Gm. sodium tetrathionate						
Before injection			48.9	34.6	14.3	
After injection			55.2	37.3	17.9	
11/29 Injection of 0.6 Gm. sodium tetrathionate						Infection clearing
Before injection			52.1	34.5	17.6	up
After injection			56.2	34.8	21.4	
	No. of Patients	No. of Tests				
Improved or recovered						
Maximum	..	..	83.8	52.6	31.2	
Minimum	..	..	37.0	20.1	5.3	
Average	15	30	50.11	33.57	16.54	
Raynaud's disease						
Maximum	..	..	52.0	29.5	31.7	
Minimum	..	..	34.4	11.9	8.0	
Average	3	6	38.77	24.80	13.97	
Senile arteriosclerosis						
Maximum	..	..	69.0	44.6	23.4	
Minimum	..	..	58.6	36.6	18.5	
Average	5	5	61.50	40.08	21.42	

compounds the reduced glutathione as well as the oxidized substance was frequently increased above normal levels. In Raynaud's disease both the reduced and the oxidized form were below normal levels. One patient with Raynaud's disease had an initial reduced glutathione

content of 11 mg. per hundred cubic centimeters of blood, which was the low level found in cases of thromboangiitis obliterans. The clinical similarity between Raynaud's disease in females and thromboangiitis obliterans in males is occasionally observed.[11]

Direct Action of the Sulfur Compounds on the Blood.—Oxygen and carbon dioxide determinations for the venous blood were made before and after addition of a few crystals of the chemical to the blood. The oxygen capacity and content thus examined in vitro were unaffected, but the carbon dioxide content was reduced. In vivo, however, the small amount of the sodium solutions injected intravenously would be insignificant in reducing the carbon dioxide content of approximately 6 quarts of blood.

Reaction of the Blood.—The actual and the theoretic p_H of the blood were frequently increased temporarily by the injection of the sulfur compounds. A rapid increase in p_H from 7.42 to 7.52 as observed in 1 clinically recovered patient with thromboangiitis obliterans could not have been due to the action of the small amount of sodium in the solution in reducing the carbon dioxide content of the blood. Changes in the oxyhemoglobin could be reflected in a shift of hydrogen ion concentration. Activation of some form of inactive oxyhemoglobin would contribute to this effect.[12] The high p_H (7.60 or more) which we reported for patients in the acute stage of thromboangiitis obliterans was found to be reduced to normal levels after intensive treatment with the inorganic sulfur compounds.

Blood Counts.—The immediate effect of the inorganic sulfur compounds on the erythrocyte counts was studied in 30 cases. The results showed no constant change. Polycythemic counts, however, returned to normal after intensive treatment. The high erythrocyte counts and hemoglobin values were probably compensatory adjustments for a deficiency in available oxygen.[13]

	Erythrocyte Counts per Cubic Millimeter of Blood (30 Patients)		
	Maximum	Minimum	Average
Before injection	5,640,000	3,680,000	4,830,000
After injection	5,850,000	3,570,000	4,776,000

11. Reid, M. R.: The General Care of Peripheral Vascular Diseases, Ann. Surg. **96**:733-743 (Oct.) 1932. Homans.[1a]

12. Litarczek, G.; Aubert, H., and Cosmulesco, I.: Studies on the Mechanism of the Reaction of Glutathione on the Dissociation Curve of Oxyhemoglobin, Compt. rend. Soc. de biol. **109**:781-783, 1932.

13. Barcroft, J.: The Respiratory Function of the Blood: I. Lessons from High Altitudes, London, Cambridge University Press, 1925.

Excretion of Sulfate in the Urine.—Thiosulfate is rapidly oxidized in the body and largely excreted in the urine as sulfate. Holbøll [14] reported that 60 to 70 per cent is thus eliminated, and Walko [15] found 50 to 70 per cent in the urine. This rapid elimination offers an expla-

TABLE 5.—*Effect of Intravenous Injections of Sodium Thiosulfate and Sodium Tetrathionate on Excretion of Sulfates in the Urine*

Twenty-Four Hour Specimens	Urine Volume, Cc.	Inorganic Sulfates	Total Sulfates
Controls			
Mr. M. No injection	1,400	1.0556	1.1592
Mr. O. No injection	1,000	1.2480	1.3420
Composite specimen (aver. of 12 patients; no injection)	2,674	1.2957	1.3589
Mr. V.			
5/18/37 No injection	510	0.6100	0.6798
5/19/37 2 Gm. sodium thiosulfate	610	1.8950	1.9154
5/20/37 0.885 Gm. sodium tetrathionate	300	0.5112	0.5208
Thromboangiitis obliterans			
Mr. N.			
4/28/37 0.885 Gm. sodium tetrathionate	1,400	1.5344	1.8088
4/29/37 No injections; smoking cigaret	2,200	1.5942	1.7248
4/30/37 2 Gm. sodium thiosulfate	2,500	2.1800	2.3850
5/ 1 37 No injection; no smoking	3,500	1.5820	1.7150
Mr. B.			
6/16/37 No injection	2,100	.....	2.1570
6/17/37 2 Gm. sodium thiosulfate	3,425	.....	3.2226
6/20/37 2 Gm. sodium thiosulfate	3,350	.....	3.7452
6/23/37 0.885 Gm. sodium tetrathionate	3,375	.....	3.6967
6/24/37 2 amp. of 0.885 Gm. sodium tetrathionate	2,275	.....	3.1300
Individual Specimens			
Thromboangiitis obliterans			
Mr. M. 5/20/37 0.885 Gm. sodium tetrathionate			
Before injection	270	0.0292	0.0443
After injection, ½ hour	285	0.0410	0.0467
2½ hours	465	0.1711	0.2362
Mr. N. 5/4/37 1 Gm. sodium thiosulfate			
Before injection	50	0.0570	0.0672
After injection, 1 hour	50	0.2174	0.2332
5/8/37 1 Gm. sodium thiosulfate			
Before injection	50	0.0804	0.0832
After injection, 1 hour	75	0.2361	0.2463
1½ hours	250	0.1060	0.1150
2 hours	300	0.0996	0.1008
5/12/37 0.885 Gm. sodium tetrathionate			
Before injection	50	0.0834	0.0922
After injection, 1½ hours	50	0.2480	0.2726
3 hours	50	0.2300	0.2324
5/13/37 0.885 Gm. sodium tetrathionate			
Before injection	77	0.1029	0.1141
After injection, 2 hours	68	0.3370	0.3467
Mr. B. 5/20/37 2 Gm. sodium thiosulfate			
Before injection	315	0.1551	0.1915
After injection, ¾ hour	135	0.2084	0.2392
2½ hours	285	0.1915	0.2383

* One gram of the thiosulfate ($Na_2S_2O_3$, 5 H_2O) contains 0.258 Gm. of sulfur, and 0.885 Gm. sodium tetrathionate ($Na_2S_4O_6$,H_2O) contains 0.393 Gm. of sulfur.

nation for the transitory effect of the thiosulfate solution on the peripheral temperatures, pulse rate and blood pressure.

14. Holbøll, S. A.: Quantitative Determinations of Sodium Thiosulphate in the Urine, Klin. Wchnschr. **4**:1636-1640 (Aug. 20) 1925.

15. Walko, K.: Concerning the Removal of Poisons by Oxidizing Agents, Arch. internat. de pharmacodyn. **4**:311-323, 1897-1898.

At the suggestion of William D. McNally, of the department of toxicology, we had prepared for us sodium tetrathionate ($Na_2S_4O_6.H_2O$), which he had found to be more beneficial than sodium thiosulfate ($Na_2S_2O_3.\ 5H_2O$) in cases of metallic poisoning. The intravenous dose (1 Gm.) of sodium thiosulfate contained 0.258 Gm. of sulfur, and the 0.885 Gm. of sodium tetrathionate injected contained 0.393 Gm. of sulfur. The results of sulfate determinations for the urine are shown in table 5.[16] The entire additional elimination after injection was in the free sulfate.[17] The remainder, present as etheral sulfate, was apparently unaffected. The volume of urine in individual specimens had no relation to the amount of sulfate eliminated, although the twenty-four hour volume indicated diuresis. No food was taken for at least four hours before the individual specimens were obtained or during the period of collection of subsequent specimens. This prevented changes in the determinations as a result of diet.

Determinations of the sulfate content of the urine immediately before and at varying intervals after injection showed that the thiosulfate solution was more rapidly eliminated than was the tetrathionate. In cases of thromboangiitis obliterans the excretion of sulfate in the twenty-four hour specimens was greater than that observed for the normal controls; the composite urine from 12 normal subjects averaged approximately the same for free and total sulfate content as did that from 2 individual patients. The more rapid excretion of the thiosulfate in the urine may account for the fact that the effect of sodium thiosulfate was more transitory than that of sodium tetrathionate.

COMMENT

The peripheral arterial occlusion associated with thromboangiitis obliterans is seldom detected until examination for arterial pulsation is made because of infection, infarcts, gangrene or acute circulatory deficiency with impending gangrene. Gross specimens of amputated extremities reveal that the occlusions have been progressive or successive. Although infection has been suspected as the cause of the disease, extensive investigations have failed to establish a bacterial cause. The significance of changes in the blood which disturb tissue metabolism and contribute to thrombosis is difficult to evaluate because of the involved physiologic processes.

16. The determinations of urine sulfate were made by Willard Bergman, assistant to Dr. William D. McNally.

17. Folin, O.: Approximately Çomplete Analysis of Thirty "Normal" Urines, Am. J. Surg. **21**:260-271 (Aug.) 1933.

Naffziger and his co-workers [18] at the University of California reported the results of their investigation of the role of sulfur in the hemorrhagic tendency associated with obstructive jaundice. They found that in obstructive jaundice, either in experimental animals or in man, the sulfur content of the venous blood is increased. They contended that certain sulfur compounds retained in the blood act as anticoagulants. Interesting and important contributions on the sulfur-containing anticoagulant heparin have been made by Best and others.[19] The role of heparin in disease conditions and the effect of therapy on the heparin content of the blood cannot be evaluated until quantitative determinations can be made. Unfortunately, no quantitative test [20] for heparin is available.

To the best of our knowledge, sodium thiosulfate was first used empirically in the treatment of thromboangiitis obliterans by Dr. Robert Johanneson, of the Presbyterian Hospital in Chicago. Although a few striking results were obtained, there was no information as to the modus operandi of the therapy or to the means of selecting patients who may be benefited. Rabinowitz [21] in 1933 and Rabinowitz and Kahn [22] in 1936 reported the presence of abnormal phospholipin metabolism and its effect on utilization of oxygen by the tissues. They were the first to report the use of sodium thiosulfate for thromboangiitis obliterans. Additional metabolic changes associated with the disease have been reported by Friedlander and Silbert [23] for cholesterol metabolism and

18. Naffziger, H. C.; Carr, J. L., and Foote, F. S.: Obstructive Jaundice, Ann. Surg. **106**:745-751 (Oct.) 1937.

19. Best, C. H.; Charles, A., and Cowan, C.: The Administration of Heparin, Proc. Am. Physiol. Soc. **119**:272-273 (May) 1937. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Baltimore, William Wood & Company, 1937. Best, C. H.: Heparin and Thrombosis, Proc. Inst. Med. Chicago **12**:210-218 (Dec. 15) 1938. Murray, D. W. G.; Jacques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Vascular Occlusion, Canad. M. A. J. **35**: 621-622 (Dec.) 1936. Best, C. H.: Heparin and Thrombosis, Proc. Staff Meet., Mayo Clin. **14**:81-84 (Feb. 8) 1939. Best, C. H., and Murray, D. W. G.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**:163-187 (Aug.) 1937. Best, C. H.; Cowan, C., and MacLean, D. L.: Heparin and Formation of White Thrombi, Science **85**:338-339 (April 2) 1937.

20. Best, C. H.: Personal communication to the authors.

21. Rabinowitz, H. M.: Thrombo-Angiitis Obliterans, Am. J. Surg. **21**:260-271 (Aug.) 1933; The Use of Sodium Iodide Thiosulphate in the Treatment of Thrombo-Angiitis Obliterans, J. Chemotherapy **13**:1-4 (April) 1936.

22. Rabinowitz, H. W., and Kahn, J.: The Relationship of Phospholipin Metabolism to Thrombo-Angiitis Obliterans and Its Treatment, Am. J. Surg. **31**:329-339 (Feb.) 1936.

23. Friedlander, M., and Silbert, S.: Thrombo-Angiitis Obliterans: VI. Chemistry of the Blood, Arch. Int. Med. **48**:500-506 (Sept.) 1931.

by Bernhard [24] for sugar metabolism. Roth, Maclay and Allen [25] found inconstant changes in serum calcium, serum protein, blood urea, serum lecithin, serum phosphorus, cholesterol and hematocrit values. The importance of these observations may be underestimated because of the difficulty in interpreting pathologic blood pictures in different stages of the disease.

Bancroft and his associates [26] have extensively investigated and reported on the use of sodium thiosulfate for thrombophlebitis. The problem studied was directed to determine the effect of sodium thiosulfate on the clotting index of the plasma and the fibrinogen content of the blood, on the assumption that, as there are definite bleeding diatheses, there are also potential "clotters." After using the thiosulfate solution prophylactically for a number of years against postoperative thrombophlebitis, Bancroft concluded that the morbidity may be definitely reduced by injections of sodium thiosulfate combined with a diet low in fats and proteins.

The changes in blood pressure, pulse and peripheral temperature seem to influence or to be affected by the available oxygen in the blood. The occasional low oxygen saturation (80 per cent) of the arterial blood in cases of thromboangiitis obliterans may be increased to normal with an accompanying elevation in blood pressure and the shunting of the peripheral circulation which follows smoking. Subsequently, the oxygen saturation was decreased by continued smoking, and this decrease may have been due to formation of inactive oxyhemoglobin. In 2 cases of thromboangiitis obliterans the oxygen capacity was only 11 volumes per cent, with 80 per cent hemoglobin (by the Dare method) and over 4,400,000 erythrocytes per cubic millimeter. Without significant changes in the hemoglobin or red cell count the oxygen capacity was increased to more than 17 volumes per cent after treatment with inorganic sulfur compounds. The presence of an unidentified form of inactive hemoglobin has just been confirmed by a report from Copenhagen, Denmark.[10]

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24. Bernhard, A.: Summary of the Chemical Blood Findings in Thrombo-Angiitis Obliterans, M. Rec. **97**:430-431 (March 31) 1920.

25. Roth, G. M.; Maclay, E. V., and Allen, E. V.: Blood in Thrombo-Angiitis Obliterans, Arch. Int. Med. **6**:413-422 (Sept.) 1938.

26. Bancroft, F. W.; Kugelmass, I. N., and Stanley-Brown, M.: Evaluation of Blood Clotting Factors in Surgical Diseases, Ann. Surg. **90**:161-189 (Aug.) 1929. Bancroft, F. W., and Stanley-Brown, M.: Postoperative Thrombosis, Thrombophlebitis and Embolism, Surg., Gynec. & Obst. **54**:898-906 (June) 1932. Bancroft, F. W.; Stanley-Brown, M., and Quick, A.: Postoperative Thrombosis and Embolism, Am. J. Surg. **28**:648-668 (June) 1933. Bancroft, F. W.; Stanley-Brown, M., and Chargaff, E.: Postoperative Thrombosis and Embolism, Ann. Surg. **106**:868-879 (Nov.) 1937.

The reports of investigations on bleeding and thrombotic diseases show a relation between the role of sulfur as used in the thiosulfate or the tetrathionate solution and the tendency to thromboses in cases of thromboangiitis obliterans. Further, the inorganic sulfur solutions have the opposite effect on the conditions studied to that of smoking, which is generally accepted as a cause of the disease. The clinical value of the inorganic sulfur solutions may be due to the fact that the effect on blood and tissue metabolism is the opposite to that observed with smoking.

SUMMARY

Sodium tetrathionate and sodium thiosulfate injected intravenously may produce a marked increase in the oxygen capacity and content of the circulating blood in some patients. This was most marked in patients with active thromboangiitis obliterans and dark, thick blood; no significant increase in the erythrocyte count or the hemoglobin value for hemoglobin accompanied the change. The presence of an inactive form of oxyhemoglobin seemed most likely to account for this effect.

In accounting for the marked increase in oxygen capacity and content of the blood of some patients after injection of inorganic sulfur, we considered three possibilities: (1) reduction of methemoglobin or of some unidentified form of inactive hemoglobin; (2) additional supply of oxygen in the sulfate (S_2O_3), or (3) increase in the oxidation catalyst, the reduced form of glutathione. We were unable to establish the presence of a known form of inactive hemoglobin, and the small amount of reducing agent was inadequate to produce the marked increase in oxygen in the approximately 6 quarts of blood. By actual determination, the sulfur compounds did not add oxygen to the blood. All evidence seemed to corroborate our findings that a catalystic action was produced by the injected chemical.

Ammundsen [10] has just reported from Copenhagen, Denmark, the presence of non-oxygen-containing hemoglobin in normal persons. Activation of this hemoglobin occurred on administration of sodium hydrosulfate. The composition of the pathologic hemoglobin and the cause for its appearance are unknown, but it is not to be assumed that all hemoglobin circulating in the blood is capable of freely combining with oxygen.

Sodium thiosulfate has been found to increase the glutathione in the liver and in the blood.[27] Glutathione, a sulfur-containing oxidation catalyst of the blood and tissues, is efficient in reducing methemoglobin,

27. Arnovljevitch, V.: Increase of Glutathione in the Liver and the Blood After Administration of Sodium Thiosulphate, Compt. rend. Soc. de biol. **106**: 681-684, 1931; Physiol. de abstr. **16**:624-626, 1931.

but spectroscopic and quantitative chemical tests have failed to detect methemoglobin as the form of inactive oxyhemoglobin present in patients with thromboangiitis obliterans.

Sodium tetrathionate had a less immediate but more prolonged effect than did sodium thiosulfate. The more rapid oxidation and excretion of the thiosulfate as free sulfate in the urine may account for this difference.

CONCLUSIONS

Intravenous injections of sodium tetrathionate and sodium thiosulfate were usually followed by increased peripheral temperatures, decreased pulse rate and reduction in blood pressure. These physiologic responses were associated with changes in the oxygen capacity and in the oxygen saturation of the arterial and the venous blood.

These effects were opposite to those that occurred with smoking, which is an important etiologic factor in thromboangiitis obliterans. The therapeutic value of sodium thiosulfate and sodium tetrathionate is probably due to the changes produced in the blood and the resulting physiologic responses.

THERAPY OF PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS

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Few conditions are as discouraging to the clinician and as unpleasant and dangerous to the patient as postoperative or postpuerperal thrombosis. There is nothing more tragic in medicine than the occurrence of a fatal pulmonary embolism in a patient who has convalesced satisfactorily after an operation and is ready to be discharged. Although less dramatic than such an outcome, persistent thrombophlebitic sequelae, such as postphlebitic edema, varicosities and ulceration, frequently cause the patient to regret having survived the original infection. All these conditions are similar in that an intravascular venous occlusion occurs, but we believe, as has been perviously emphasized,[1] that it is necessary from prognostic and therapeutic points of view to differentiate between thrombophlebitis and phlebothrombosis. In the former the intravascular clotting is associated with and dependent on inflammation of the wall of the vein, whereas in the latter there is no associated inflammatory process and because of this with absence of fixation of the thrombus to the vessel wall there is great danger of embolism. It is not the purpose of this presentation to discuss the causes of these two types of intravascular clotting. The reader is referred to previous publications.[1]

The treatment of intravascular venous thrombosis may be outlined as follows:

A. Prophylaxis
   1. Hydration
   2. Mobilization
   3. Respiratory stimulation
   4. Prevention of increased abdominal tension
   5. Application of heat (heat tent)
   6. Administration of sodium thiosulfate
   7. Hirudinization (leeches)
   8. Heparinization

From the Department of Surgery, School of Medicine, Tulane University.

1. Ochsner, A., and DeBakey, M.: Thrombophlebitis and Phlebothrombosis, South. Surgeon **8**:269, 1939.

B. Conservative therapy
   1. Immobilization and elevation
   2. Application of heat
   3. Hirudinization
   4. Application of compression bandages
   5. Vasodilatation
      a. Administration of parasympathetic stimulants
      b. Block of the sympathetic nerves with procaine hydrochloride

C. Radical therapy
   1. Ligation
   2. Excision
   3. Incision and drainage
   4. Thrombectomy and embolectomy

Institution of prophylactic measures merely signifies avoidance of those factors which may be considered as precipitating the thrombotic process. Dehydration, which may occur postoperatively and which increases the viscosity of the blood, favors thrombosis and should be combated by adequate hydration of the patient. Coller and his associates [2] have demonstrated the frequency and the degrees of postoperative dehydration. That increased viscosity of the blood may occur postoperatively has been demonstrated by Zarubin [3] and by Bolognesi.[4] Similar observations were made by Löhr and Löhr,[5] who also found that the viscosity paralleled the erythrocytic sedimentation rate. According to numerous observers,[6] increase in the globulin fraction of the

2. Coller, F. A.: Studies in Water Balance, Dehydration and Administration of Parenteral Fluids, Minnesota Med. **19**:490, 1936. Coller, F. A.; Dicks, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, J. A. M. A. **107**:1522 (Nov. 17) 1936.

3. Zarubin, cited by Matas, R.: On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain: Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of the Lesion in Its Medico-Legal Relations, Am. J. Surg. **24**:642, 1934.

4. Bolognesi, G.: Untersuchungen über die Änderungen in der Blutviskosität infolge von chirurgischen Operationen, Zentralbl. f. Chir. **36**:1161, 1909.

5. Löhr, W., and Löhr, H.: Ueber die Veränderung der physikalisch-chemischen Struktur der Blutflüssigkeit bei beschleunigter Blutkörperschensenkung im Gefolge von Reizkörpertherapie, chirurgischen Operationen und Erkrankungen, Ztschr. f. d. ges. exper. Med. **29**:139, 1922.

6. (*a*) Rohrer, F.: Bestimmung des Mischungsverhältnisses von Albumin und Globulin in Blutserum, Deutsches Arch. f. klin. Med. **121**:221, 1917. (*b*) Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1919. (*c*) Heyder, cited by Naegeli. (*d*) Linzenmeier, G.: Eine neue Schwangerschaftsreaktion und ihre theoretische Erklärung, Arch. f. Gynäk. **30**:608, 1920. (*e*) Fåhræus, R.: The Suspension-Stability of the Blood, Acta med. Scandinav. **55**:1, 1921. (*f*) Löhr and Löhr.[5]

plasma augments the viscosity. The mechanism by which increased viscosity of the plasma per se aids in production of a thrombus is probably by favoring circulatory retardation. Thus, postoperative hydration becomes an important factor in the prevention of venous thrombosis.

The importance of circulatory retardation as a cause of intravascular clotting has been repeatedly emphasized. Circulatory retardation may be due to a number of causes. Among the various factors responsible is immobility. Other factors are anatomic peculiarities, posture hypopnea and increased abdominal tension. Any condition which will interfere with normal circulation in the vascular system may act as a precipitating factor and in the presence of predisposing factors may cause thrombosis. This has been emphasized particularly by Beneke [7] and by Aschoff.[8] An anatomic factor, i. e., the peculiar relation of the left iliac vein to the right iliac artery, causing compression of the former, is uncontrollable. The other factors, however, are controllable and can be obviated. Posture may predispose to circulatory retardation. The placing of a patient in Fowler's position, with flexion of the thighs on the abdomen and flexion of the legs on the thighs at the knees, can result in compression of the vessels beneath the inguinal ligament and those in the popliteal space, respectively. Dependency of the lower extremity with the patient in the head-up (Fowler) position also predisposes to venous stasis. Cardiovascular activity is diminished postoperatively by the quiescence of the patient after an operative procedure. As the result of quiet rest in bed, the muscles of the extremities are relaxed, and return of venous blood to the heart is less rapid than normal. Circulatory activity is further decreased by peripheral vasoconstriction; this has been emphasized by Leriche [9] and by Kvale.[10] Because of vasoconstriction in the capillary bed, venostasis occurs, which in turn predisposes to thrombosis. For these reasons, early postoperative mobilization in cases of venous thrombosis is essential as a prophylactic measure. Ries,[11]

7. Beneke, R.: Die Thrombose, in von Jagic, N.: Handbuch der allgemeinen Pathologie, Diagnostik und Therapie der Herz- und Gefässerkrankungen, Leipzig, Franz Deuticke, 1913, vol. 2, pt. 2, pp. 130-299.

8. Aschoff, L.: Thrombosis, in Lectures on Pathology, New York, Paul B. Hoeber, 1924.

9. Leriche, R.: Des moyens de réduire au minimum la maladie post-opératoire. De l'opératoire sous rayons infra-rouges, Rev. de chir. **74**:99, 1936.

10. Kvale, cited by Ward, C. E., and Horton, B. T.: Postoperative Thrombophlebitis of the Inferior Vena Cava in a Child, Proc. Staff Meet., Mayo Clin. **12**:811, 1937.

11. Ries, E.: Some Radical Changes in the After Treatment of Celiotomy Cases, J. A. M. A. **33**:454 (Aug. 19) 1899.

Richardson,[12] Boldt [13] and others [14] were early advocates of movement of the legs while the patient is in bed. More recently, the significance of such exercise has been emphasized again.[15] Patients should be instructed to move their extremities frequently—as Wangensteen [16] has suggested, at least a thousand times a day. Gamble [17] has devised a bed bicycle for this purpose. Patey [18] advocated placing the patient in the head-up position with a board under the feet to produce increased muscular tension.

Normal negative pressure within the thorax favors return of venous blood to the cardiac chambers. Because of the diminished respiratory activity which follows operation, there is interference with the normal venous return. Moreover, hypopnea occurs postoperatively as the result of pain caused by movement of the abdominal muscles and increase in abdominal tension. It has been shown repeatedly that postoperatively the diaphragmatic excursions are diminished, which results in concomitant increase in the intrapleural pressure, venous stasis and circulatory

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12. Richardson, M. H.: On Certain Unavoidable Calamities Following Surgical Operations, Boston M. & S. J. **151**:583, 1904.

13. Boldt, H. J.: The Management of Laparotomy Patients and Their Modified After Treatment, New York M. J. **85**:145, 1907.

14. (*a*) Henle, cited by Pool.[14e] (*b*) Krecke, A.: Ueber Vor- und Nachbehandlung bei Bauchoperativen insbesondere über das frühzeitige Aufstehenlassen, München. med. Wchnschr. **57**:2037, 1910. (*c*) Wilson, L. B.: Fatal Post-Operative Embolism, Ann. Surg. **56**:809, 1912. (*d*) Kleinschmidt, O.: Die Nachbehandlung Laparotomierter, Ergebn. d. Chir. u. Orthop. **5**:432, 1913. (*e*) Pool, E. H.: Systematic Exercises in Postoperative Treatment, J. A. M. A. **60**:1202 (April 19) 1913. (*f*) Vietor, J. A.: Clinical Consideration of Thrombosis and Embolism, Ann. Surg. **82**:193, 1925.

15. (*a*) Schmid, H. H.: Verhütung von postoperativen Thrombosen und Embolien, Zentralbl. f. Gynäk. **61**:307, 1937. (*b*) Voegt, H.: Veränderungen der Wadenmuskulatur bei Venenthrombose und langem Krankenlager, Virchows Arch. f. path. Anat. **300**:190, 1937. (*c*) Knott, W.: Ueber die Verhütung von postoperativen Thrombosen und Embolien durch die Hochlagerung nach H. H. Schmid, Zentralbl. f. Gynäk. **62**:679, 1938. (*d*) Shaw, W. F., and Rickard, C. E. B.: Postoperative Exercises as Preventive of Embolism, J. Obst. & Gynaec. Brit. Emp. **45**:451, 1938.

16. Wangensteen, O.: The Therapeutic Problem in Bowel Obstruction, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

17. Gamble, H. A.: The Prevention of Postoperative Embolism and Phlebitis, Am. J. Surg. **28**:93, 1935.

18. Patey, D. H.: Artificially Induced Thrombophlebitis, Surg., Gynec. & Obst. **64**:1002, 1937.

retardation.[19] Prevention of hypopnea is therefore important, and patients should be instructed to take deep breaths frequently during their waking hours. It is the custom in our clinic to have a patient take at least ten deep breaths every hour. If the patient will not do this voluntarily, it can be accomplished by the use of carbon dioxide inhalations.[20] Increased intra-abdominal pressure also favors circulatory retardation by exerting pressure on the intra-abdominal veins, interfering with the return flow of venous blood from the lower extremity. Increased intra-abdominal tension may result from a number of factors, such as application of constricting bandages, which are frequently used by surgeons in an attempt to give support to the abdominal wall, and functional inactivity of the gastrointestinal tract, with its associated accumulation of fluid and gas in the intestine and stomach (ileus). For this reason, the increased intra-abdominal tension resulting from tight bandages or from ileus should be combated by avoidance of tight dressings, by use of appropriate devices, such as the indwelling catheter, and by other methods previously described.[21] As was shown by Patey,[19f] there is definitely increased intra-abdominal tension after an operation, apparently due to the decreased action of the diaphragm and splinting of the abdominal wall (presumably because of pain occasioned by movement).

Application of heat in the form of a heat tent to the lower part of the abdomen is undoubtedly of value after an operation, not only because of its beneficial effect on the tone of the intestine but probably because it produces vasodilatation of the peripheral vessels. The extremely low incidence of intravascular clotting in our clinic is due, we believe, to the fact that heat tents are routinely applied to the abdomen postoperatively. As these tents are large and cover the entire lower portion of the body, applying as much heat on the lower extremities as on the abdomen, we

19. (*a*) Pasteur, W.: Massive Collapse of the Lung, Lancet **2**:1351, 1908. (*b*) Churchill, E. D., and McNeil, D.: The Reduction in Vital Capacity Following Operations, Surg., Gynec. & Obst. **44**:483, 1927. (*c*) The Reduction in Vital Capacity, Boston M. & S. J. **197**:83, 1927. (*d*) Muller, G. P.; Overholt, R. H., and Pendergrass, E. P.: Postoperative Pulmonary Hypoventilation, Arch. Surg. **19**:1322 (Dec., pt. 2) 1929. (*e*) Brunn, H.: Atelectasis: A Review of Its History, Significance and Treatment, West. J. Surg. **38**:647, 1930. (*f*) Patey, D. H.: The Effect of Abdominal Operations on the Mechanism of Respiration, with Special Reference to Pulmonary Embolism and Massive Collapse of the Lungs, Brit. J. Surg. **17**:487, 1930. (*g*) Carlson, H. A.: Inhibition of Respiration as a Factor in the Pathogenesis of Postoperative Pulmonary Complications, J. Thoracic Surg. **2**:196, 1932. (*h*) Prinzmetal, M.; Brill, S., and Leake, C. D.: Postoperative Pulmonary Subventilation, Surg., Gynec. & Obst. **56**:129, 1933.

20. von Seeman, H.: Operation und Gewebeschonung: II. Beziehungen zwischen Operationswunde und Entstehung, Vermeidung und Bekämpfung der mittelbaren Operationschädigungen (spontane Venenthrombose und Pneumonie), Deutsche Ztschr. f. Chir. **223**:85, 1930. Gamble.[17] Knott.[15e]

21. Ochsner, A.: Postoperative Treatment, South. M. J. **29**:53, 1936.

feel that the associated vasodilatation aids in preventing circulatory retardation.

The use of sodium thiosulfate postoperatively as suggested by Bancroft and his associates [22] for prevention of thrombosis may also be of value. This author and his co-workers, working on the theory that since there are potential "bleeders" there are potential "clotters," have devised a test for the plasma clotting index and one for fibrinogen. The prothrombin test, designated as the test for the plasma clotting index, is indicative of clotting tendencies when infection is at a minimum, while the fibrinogen test may suggest infection and the likelihood of thrombophlebitis. If examination of blood taken either preoperatively or postoperatively shows a high plasma clotting index and a high fibrinogen content, 10 cc. of a 10 per cent solution of sodium thiosulfate is administered intravenously on three successive days, the series being repeated after an interval of one day if the bleeding factors remain high. These authors have reported a large series of cases in which this procedure was followed by no thromboembolic accident.

Hirudinization and heparinization are also prophylactic measures based on anticoagulant activity. The former has been emphasized by one of us (Ochsner) in collaboration with Mahorner [23] and more recently by Chalier [24] and Rouhier.[25] Crafoord [26] and Murray and Best and their co-workers [27] have reported interesting experimental and clinical investigations on the use of heparin in prevention of thromboembolic phenomena. These investigators found experimentally that by administering purified heparin intravenously over a period of hours it was possible to diminish the coagulation time considerably. They have applied the results of their investigations to human beings, and, although

22. (*a*) Bancroft, F. W.; Stanley-Brown, M., and Quick, A. J.: Postoperative Thrombosis and Embolism, Am. J. Surg. **28**:648, 1935. (*b*) Bancroft, F. W.; Stanley-Brown, M., and Chargaff, E.: Postoperative Thrombosis and Embolism, Ann. Surg. **106**:868, 1937.

23. Ochsner, A., and Mahorner, H.: The Use of Leeches in the Treatment of Phlebitis and the Prevention of Pulmonary Embolism, Ann. Surg. **98**:408, 1933.

24. Chalier, A.: La prévention et le traitement abortif des phlébites post-opératoires, Presse méd. **46**:1345, 1938.

25. Rouhier, G.: A propos de l'utilisation des sangsues comme préventif des phlébites post-opératoires, Mém. Acad. de chir. **64**:356, 1938.

26. Crafoord, C.: Preliminary Report on Postoperative Treatment with Heparin as a Preventive of Thrombosis, Acta chir. Scandinav. **79**:407, 1937; Heparin and Post-Operative Thrombosis, ibid. **82**:319, 1939.

27. Murray, D. W. G.; Jaques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**:163, 1937. Murray, D. W. G., and Best, G. H.: Heparin and Thrombosis: Present Situation, J. A. M. A. **110**:118 (Jan. 8) 1938. Best, C. H.: Heparin and Thrombosis, Brit. M. J. **2**:977, 1938.

an insufficient number of cases have been studied, the results have been satisfactory. Murray and Best have used a "saline and heparin mixture" which was allowed to run into the vein slowly, so that the clotting time of the patient's blood was maintained at about fifteen minutes. However, they stated that injection of heparin is now being restricted to cases in which extensive surgical procedures have been carried out and in which thrombosis is likely to occur.

CONSERVATIVE THERAPY

Immobilization and Elevation of the Extremity.—This is a time-honored method of treatment of thrombophlebitis. Its rational basis is the placing of the part at physiologic rest to minimize the danger of breaking off of an embolus and to relieve edema by favoring lymphatic flow. This form of therapy has a number of advocates.[28] A satisfactory method of immobilizing the entire extremity consists of applying a large sheet wadding dressing from the tips of the toes to the groin. Elevation of the extremity is accomplished either by elevation of the foot of the bed or by placing the involved extremity in a sling, on an inclined plane or on pillows. Heat may be applied in the form of a heat tent or by hot compresses. The purpose of application of external heat is to hasten the normal involution of the thrombus and periphlebitis, i. e., the inflammatory changes.

Hirudinization.—Revival of the treatment of thrombophlebitis by leeches is credited primarily to Termier,[29] of France. In 1922 he[30] reported 19 cases, and three years later, 73 cases, of phlebitis treated by this form of therapy, with remarkable relief of acute manifestations. Subsequently, extensive reports appeared in the literature, especially in

28. (*a*) De Treigny, M.: For How Long Must a Case of Phlebitis Be Immobilized? Internat. Clin. **10**:75, 1900. (*b*) Van der Veer, A.: Phlebitis Following Abdominal Operations, Tr. Am. Surg. A. **19**:223, 1901. (*c*) Brothers, A.: The Prophylaxis and Treatment of Postoperative Phlebitis, Am. J. Obst. **55**:609, 1907. (*d*) Reisman, D.: Phlebitis and Thrombosis, M. Clin. North America **4**:1005, 1921. (*e*) Bain, W.: Phlebitis of the Lower Extremities and Superficial Veins of the Abdomen, Lancet **1**:701, 1927. (*f*) Brown, G. E.: Postoperative Phlebitis: Clinical Study, Arch. Surg. **15**:245 (Aug.) 1927. (*g*) Rabinowitz, M. A., and Holtzman, I. N.: Early Recognition of Peripheral Venous Thrombosis, New York State J. Med. **34**:973, 1934. (*h*) Homans, J.: Venous Thrombosis in the Lower Limbs: Its Relation to Pulmonary Embolism, Am. J. Surg. **38**:316, 1937. (*i*) McNealy, R. W.: Treatment of Phlebitis, S. Clin. North America **17**:523, 1937.

29. Termier, J.: Traitement abortif des phlébites chirurgicales avec lever précoce, Proc.-verb. et mém. Cong. franç. de chir. **31**:949, 1922.

30. Termier, J.: Grenable-Abortive Treatment of Surgical and Obstetrical Phlebitis Through Hirudinization (Application of Leeches), Proc.-verb. et mém. Cong. franç. de chir. **34**:434, 1925.

Europe, praising the brilliant results following this method of therapy.[31] Considerable experimental and clinical work with leeches has been done in the United States by one of us (Ochsner) with Mahorner.[32] The leech's salivary gland secretes hirudin, which can completely prevent the coagulation of blood and in vitro has been observed to cause dissolution of a blood clot. Indeed Termier concluded that the power of this substance to dissolve a blood clot explains the excellent effect obtained in

31. (*a*) Julliard: Traitement de la thrombo-phlébite post-opératoire des membres inférieurs, Schweiz. med. Wchnschr. **55**:515, 1925. (*b*) Gonnet; Jeannin, and Josserand: De l'usage des sangsues dans les phlébites puerpérales, Lyon méd. **138**:657, 1926. (*c*) Beguier: Thrombo-phlébite du membre inférieur. Traité avec succès par les applications de sangsues, Arch. méd.-chir. de Province **17**:109, 1927. (*d*) Hamm, A., and Schwartz, A.: De l'emploi des sangsues dans le traitement des phlébites, Schweiz. med. Wchnschr. **57**:1125, 1927. (*e*) Monzon, J.: Le traitement des phlébites thrombosantes par les sangsues, Presse méd. **35**:677, 1927. (*f*) Tholen, G. A.: Die Behandlung post-operativen und puerperalen Thrombosen und Embolien, Wien. klin. Wchnschr. **42**:1107, 1927. (*g*) ten Berge, B. S.: Leeches in Venous Infections: Case, Nederl. tijdschr. v. geneesk. **1**:2893, 1928. (*h*) Chavannay, J., and Magnant, J.: À propos du traitement des phlébites oblitérantes par l'hirudinisation, Rev. de chir. **66**:461, 1928. (*i*) Ducuing, J.: Pourquoi le traitement des phlébites chirurgicales par les sangsues semble-t'il donner de bons résultats? Progrès méd. **43**:1787, 1928. (*j*) Ichok, G.: El empleo de las sanguijuelas en el tratamiento de las flebitis, Arch. de med., cir. y especialid. **28**:747, 1928. (*k*) di Pace, I.: La irudinizzazione delle flebiti, Gazz. d. osp. **49**:73, 1928. (*l*) Vidal: Traitement par des applications de sangsues d'un cas de phlébite puérperale à début embolique, Bull. Soc. d'obst. et de gynéc. **17**:36, 1928. (*m*) Coggi, C.: A proposito dell irudinizzazione delle thromboflebiti in ostetricia e ginecologia, Ann. di ostet. **51**:1457, 1929. (*n*) Mureşanu, B.: Clinical Considerations on the Treatment of Post-Operative Phlebitis with Leeches, Rev. de chir., Bucuresti **21**:592, 1929. (*o*) Sulger, E., and Boszin, T.: Ueber die post-operative Thrombose und Embolie sowie ihre therapeutische und prophylaktische Behandlung mit Blutegeln, Deutsche Ztschr. f. Chir. **216**:175, 1929. (*p*) Mayer, L.: À propos de l'embolie post-opératoire, Bruxelles méd. **10**:312, 1930. (*q*) Angeli, A.: La irudinizzazione nelle flebiti, Rassegna internaz. di clin. e terap. **12**:1180, 1931. (*r*) Chalier, A.: Sur la prophylaxie des phlébites et embolies postopératoires en gynécologie, Bull. et mém. Soc. nat. de chir. **57**:216, 1931. (*s*) Dimitriu, V., and Somnea, G. O.: Action thérapeutique de l'hirudine dans les phlébites, la septicémie et dans quelques affections de nature microbienne, Presse méd. **39**:1359, 1931. (*t*) Rossi, G.: La irudinizzazione nelle flebiti postoperatorie e puerperali, Policlinico (sez. prat.) **38**:989, 1931. (*u*) Oden, H. G.: Zur Blutegeltherapie der Thrombophlebitis, Med. Welt **7**:273, 1933. (*v*) Straaten, T.: Die Blutegeltherapie der Thrombose, Deutsche Ztschr. f. Chir. **238**:513, 1933. (*w*) de Donno, E.: Sulla terapia delle thromboflebiti puerperali e postoperatorie con la fasciatura con cerotto, Clin. ostet. **36**:647, 1934. (*x*) Haupt, W.: Zur Thrombosenbehandlung und—Verhütung mittels Blutegel, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1934, p. 189. (*y*) Hauptstein, P.: Die Blutegelbehandlung der Thrombophlebitis (Thrombose) nach Operationen und im Wochenbett, Med. Welt **8**:1723, 1934. (*z*) Hempel, C.: Die medizinische Anwendung des Blutegels im Wandel der Zeiten

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cases of thrombophlebitis. Others have suggested as an explanation for the good results observed from this form of therapy an increase in phagocytic and bactericidal powers,[33] local blood letting,[31c] prevention of venous spasm [31d] and general hirudinization.[34]

The efficacy of this form of therapy in cases of phlebitis has been reported by numerous investigators. In 1933, one of us (Ochsner) in collaboration with Mahorner [23] reported 3 cases of phlebitis and 1 of thromboangiitis obliterans in which it was used and was followed by rapid abatement of symptoms. Recently, Lilienthal,[35] Magnus [36] and Pardella [37] have also reported good results. Chalier [24] and Rouhier [25] have recently reported its use as a preventive measure. Rouhier [25] stated, however, that once thrombophlebitis occurs the leeches should not be applied, because of the possibility of development of an embolism. Moulonguet [38] and Ameline [39] also stated that they have given up the use of leeches for phlebitis because of the occurrence of emboli after their application. We have never observed any bad results from the use of leeches, however, and we still believe that there are many conditions, such as portal thrombophlebitis (pylephlebitis), in which hirudinization is one of the most valuable methods of therapy, if not the most valuable.

Heparinization.—Heparin has been used in the treatment of thrombophlebitis. Murray and Best and their associates [27] reported 28 cases in which it was employed. They observed no evidence of embolism in any of these. The clinical signs and symptoms, pain, swelling, tenderness and fever, appeared to show more rapid improvement than was observed in a control group.

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mit neueren Daten aus Zoologie, Physiologie und Pharmakologie, ibid. **8**:210, 1934. (*a*[1]) Macciotta, M.: L'irudinizzazione nelle flebiti e nelle forme inflammatorie ginecologiche, Clin. ostet. **36**:36, 1934. (*b*[1]) Pascalis, G.: Chirurgie pelvienne et phlébites, Rev. gén. de clin. et de thérap. **48**:279, 1934. (*c*[1]) Bolli, E. V.: Il metodo Termier nella cura delle flebiti puerperali e postoperatorie: Rassegna bibliografica e contributo personale, Arch. di ostet. e ginec. **42**:475, 1935. (*d*[1]) Meyer, E.: Die Blutegelbehandlung von Thrombosen und Thrombophlebitiden, Therap. d. Gegenw. **76**:18, 1935. (*e*[1]) Leuze, A. M.: Technik der Blutegelbehandlung, München. med. Wchnschr. **83**:315, 1936. (*f*[1]) Rüdiger: Zur Blutegelbehandlung, ibid. **83**:1276, 1936. (*g*[1]) Wimhöfer, H.: Die Bedeutung der Blutegelbehandlung in der Therapie und Prophylaxe der postoperativen Thrombose, Ztschr. f. Geburtsh. u. Gynäk. **117**:397, 1938.

32. Ochsner, A., and Mahorner, H.: Bactericidal Effect of Hirudin and Heparin: I. Intravenous Injection of Hirudin and Heparin and Leeching in Experimental Bacteremia, Arch. Surg. **31**:308 (Aug.) 1935. Mahorner, H., and Ochsner, A.: Bactericidal Effect of Hirudin and Heparin: II. Growth of Organisms in Blood Rendered Incoagulable with Hirudin and Heparin, ibid. **31**: 371 (Sept.) 1935. Footnote 23.

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Compression Bandages.—Application of compression devices, such as elastic adhesive plaster or Unna's paste boot, has also been advocated for treatment of thrombophlebitis. Fischer [40] is usually credited with being the first to advocate this form of therapy for the early stages of the disease, although Rupp [41] had previously advocated it as a prophylactic measure. This method of therapy has recently received considerable approbation by Friedländer,[42] Müller,[43] Stotzer [44] and Pratsicas and Théohari.[45]

Vasodilatation.—The use of vasodilatory measures in the treatment of thrombophlebitis has recently received considerable attention. Murphy [46] and, more recently, Sokolov and Meyers [47] have advocated iontophoresis with acetylbetamethylcholine hydrochloride (mecholyl). Murphy reported favorable results with this form of therapy in 33 cases of thrombophlebitis. Nineteen patients with thrombophlebitis of the deep veins were treated by this method by Sokolov and Meyers, and improvement was noted in 18. However, only 3 of these were in the acute stages, although the authors stated that the best improvement was obtained in the cases of acute involvement. Vasodilation by means of artificially induced fever has been suggested by Eveymeersch and Snoeck [48] and by Pitfield.[49] The former authors used injections of sterile milk to produce the fever, and the latter author used injection of typhoid vaccine. Irradiation therapy has also been suggested, by Halban [50] and by Henschen and Becker.[51] Paine and Levitt [52] have recently reported the use of intermittent venous occlusion in the treatment of thrombophlebitis. This method of therapy was employed in 4 cases of acute thrombophlebitis and in 7 of the chronic form, with relief of pain, tenderness and discomfort. Edema was decreased in some cases and unaffected in others.

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33. Bosc, F. J., and Delezenne: De l'immunité conférée par quelques substances anticoagulantes; de son méchanisme; excitation de la phagocytose, augumentation du pouvoir bactéricide du sang, Compt. rend. Acad. d. sc. **123**:500, 1896.

34. Henschen, cited by Sulger and Boszin.[31o]

35. Lilienthal, H., in discussion on Bancroft, Stanley-Brown and Chargaff.[22b]

36. Magnus, G.: Blutegelbehandlung bei Thrombosebereitschaft, München. med. Wchnschr. **84**:1992, 1937.

37. Pardella, C.: Sulla cura delle trombose e delle thromboflebiti degli arti, Ann. di ostet. e ginec. **60**:973, 1938.

38. Moulonguet, in discussion on Rouhier.[25]

39. Ameline, in discussion on Rouhier.[25]

40. Fischer, cited by Friedländer.[42]

41. Rupp: Zur Verhütung postoperativer Thrombophlebitis, Zentralbl. f. Chir. **58**:1444, 1931.

42. Friedländer, E.: Die Kompressionsbehandlung der Venenentzündung, Wien. klin. Wchnschr. **48**:791, 1935.

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In our experience, the best method of therapy and the one which has given by far the best results is production of vasodilatation passively by blocking with procaine hydrochloride the regional sympathetic ganglions, as suggested by Leriche.[53] In 1934, Leriche and Kunlin[54] reported 3 cases of acute postoperative phlebitis successfully treated by procaine hydrochloride block of the lumbar sympathetic ganglions. Since then Kunlin, Leriche and others[55] have reported other cases in which similar results were obtained. Numerous other reports[56] attest the success of this method of therapy. According to Leriche and Kunlin,[57] the mechanism of development of clinical manifestations of

43. Müller, A.: Die Thrombophlebitis und ihre Behandlung mit komprimerendem Gehverband, Med. Klin. **33**:793, 1937.

44. Stotzer, E.: Zur Phlebitis und deren ambulanten Behandlung, Schweiz. med. Wchnschr. **67**:476, 1937.

45. Pratsicas, A., and Théohari, C.: La traitement de la phlébite aiguë des membres inférieurs par la compression précoce, J. de méd. de Lyon **19**:367, 1938.

46. Murphy, H. L.: Treatment of Thrombophlebitis with Acetyl-Beta-Methyl Choline Chloride Iontophoresis, Surg., Gynec. & Obst. **65**:100, 1937.

47. Sokolov, R. A., and Meyers, M. P.: The Treatment of Deep Thrombophlebitis and Chronic Leg Ulcers with Acetyl-Beta-Methyl Choline Chloride Iontophoresis, Am. Heart J. **17**:316, 1939.

48. Eveymeersch, A., and Snoeck, J.: Essai de protémothérapie non-spécifique dans les phlébites aiguës du post-partum (injections de lait), Bruxelles méd. **15**: 98, 1934.

49. Pitfield, R. L.: Induction of Therapeutic Crises by Typhoid Vaccine in Septic Phlebitis, M. Rec. **145**:147, 1937.

50. Halban, cited by McNealy.[281]

51. Henschen, C., and Becker, F.: Röntgenbestrahlung der akuten, der subakuten und der chronischen Phlebitis und Thrombophlebitis, Schweiz. med. Wchnschr. **67**:438, 1937.

52. Paine, J. R., and Levitt, G.: The Treatment of Thrombophlebitis of the Deep Veins of the Lower Extremities with Intermittent Venous Occlusion, Surgery **5**:707, 1939.

53. (*a*) Leriche, R.: Traitement chirurgical des suites éloignées des phlébites et des grands oedèmes non médicaux des membres inférieurs, Bull. et mém. Soc. nat. de chir. **53**:187, 1927; (*b*) Sur l'importance de la périphlébite dans la genèse des accidents tardifs, consécutifs aux oblitérations veineuses, ibid. **53**:561, 1927. (*c*) Leriche, R., and Kunlin, J.: Traitement immédiat des phlébites post-opératoires par l'infiltration novocaïnique du sympathique lombaire, Presse méd. **42**:1481, 1934.

54. Leriche, R., and Kunlin, J.: Tratamiento immediato de las flebitis post-operatorias por la infiltración novocainica del simpático lumbar, Crón. méd. mex. **33**:389, 1934; footnote 53 *c*.

55. (*a*) Kunlin, J., and Lucinesco, E.: Résultats du traitement immédiat des phlébites post-opératoires et varique-uses par l'infiltration novocaïnique du sympathique lombaire: Cinq nouvelles observations, Bull. et mém. Soc. nat. de chir. **61**: 965, 1935. (*b*) Houot, A.: Infiltrations stellaires dans une thrombophlébite du membre supérieur par effort, Progrès méd., 1937, p. 492. (*c*) Leriche, R.: Considérations sur le traitement chirurgical de la phlébite du membre inférieur et de ses séquelles éloignées, J. internat. de chir. **3**:585, 1938.

thrombophlebitis is the initiation of a vasomotor reflex as the result of impulses originating in the thrombosed venous segment (fig. 1). Apparently, Leriche [55c] is of the opinion that there are three prominent factors in this process, namely, venospasm, coagulation and arterial spasm. By block of the sympathetic ganglions with procaine hydrochloride this vasomotor reflex is broken, and the clinical manifestations are relieved (fig. 2).

We [58] have shown by clinical and experimental observations that vasospasm resulting from impulses originating from involved venous segments is one of the most important factors in the production of the clinical manifestations of thrombophlebitis. Such vasospastic influences probably affect both arterioles and veins (figs. 1 to 3). Numerous investigators [59] have shown that a localized thrombophlebitic process can initiate a marked vasospasm. Indeed, the vasospasm may be so

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56. (*a*) Bourgalt, E.: Traitement des phlébites par anesthésies temporaires de la chaine sympathique lombaire, J. de l'Hôtel-Dieu de Montréal **4**:212, 1935. (*b*) Aufrère and Mathieu: L'infiltration du sympathique lombaire dans le traitement immédiat des phlébites post-opératoires, Lyon méd. **158**:169, 1936. (*c*) Digonnet; Chenebault, and Rouchy: Deux cas de phlébite puerpérale, traités par novocaïnisation du sympathique lombaire, Bull. Soc. d'obst. et de gynéc. **25**:215, 1936. (*d*) de Scuza Rudge, W.: Tratamento immediato das phlebites post-operatorias pela infiltraçao novocainica do sympathico lombar, Rev. de gynec. e d'obst. **30**:833, 1936. (*e*) de Oliveira Figueiredo, I.: Tres casos de phlebites puerperaes tratados pelo methodo de Leriche, ibid. **31**:199, 1937. (*f*) Massart, R.: L'infiltration analgésique des ganglions sympathiques in particulier du ganglion étoilé et du deuxième ganglion lombaire (étude d'une centaine de cas), Bull. et mém. Soc. de chir. de Paris **29**:91, 1937. (*g*) Caeiro, J. A.: La sección funcional del simpático por la novocainización del ganglio estelar y del simpático lumbar: Técnica de la inyección, Día méd. **10**:779, 1938. (*h*) Fasano, M.: La cura della flebite post-operatoria con il metodo di Leriche, Boll. e mem. Soc. piemontese de chir. **8**:61, 1938. (*i*) Grégoire, R.: La répercussion de l'inflammation des veines sur le système artériel collatéral, Mém. Acad. de chir. **64**:363, 1938. (*j*) Demarez, R., and Linquette, M.: Le traitement immediat des phlébites post-opératoires par l'anesthésie du sympathique lombaire; à propos de quatre observations personelles, Echo méd. du Nord **10**:12, 1939.

57. Leriche and Kunlin.[53e] Leriche and Kunlin.[54] Leriche.[55c]

58. (*a*) DeBakey, M.; Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, Proc. Soc. Exper. Biol. & Med. **41**:585, 1939. (*b*) Ochsner, A., and DeBakey, M.: Thrombophlebitis: The Role of Vasospasm in the Production of the Clinical Manifestations, J. A. M. A. **114**:117 (Jan. 13) 1940.

59. (*a*) Pallin, G.: The Differential Diagnosis: Arterial Embolism, Venous Thrombosis, Acta chir. Scandinav. **65**:558, 1929. (*b*) Trémolières, F., and Véran, P.: Syndrome d'oblitération artérielle du membre inférieur droit apparu au cours d'une phlébite superficielle et profonde avec embolies pulmonaires. Effet thérapeutique de l'acétycholine, Bull. méd., Paris **43**:1101, 1929. (*c*) Läwen, A.: Arteriospasmus bei akuter massiver Thrombose der V. femoralis, Zentralbl. f.

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marked that the condition appears to be arterial embolism,[60] and in some instances actual gangrene [61] has occurred. We have conducted experiments on animals which show convincingly that localized chemical endophlebitis may produce such marked arteriolar vasospasm that practically all pulsation disappears. Moreover, it is possible to demonstrate that this mechanism is the result of vasoconstrictor impulses originating in the involved segment and transmitted over the sympathetic nervous system (fig. 3). In another publication [58] we have reviewed the mechanism by which vasospasm in thrombophlebitis can produce edema. Briefly, the factors which result from vasospasm and increase the amount of perivascular fluid are: (1) increased filtration pressure, (2) anoxia of the capillary endothelium and (3) diminution in the flow of lymph. We have determined the venous pressure in 8 cases and found it to be four to five times that of normal (fig. 3). This increase in venous pressure obviously increases the filtration pressure, which favors transudation of the fluid from the vascular into the perivascular spaces. Because of the associated arteriolar spasm and evidences of diminished vascularity, there probably occurs a relative anoxia of the capillary endothelium, favoring increased permeability of this membrane and consequent increased transudation of vascular fluid into the perivascular spaces. That edema is greatly influenced by the presence or absence of normal arteriolar pulsations has been demonstrated by the experiments of McMaster and Parsons [62] and by those of Cressman and Blalock,[63]

Chir. **61**:1681, 1934. (*d*) Audier, M.: La symptomatologie artérielle des phlébites des membres et de leurs séquelles, Progrès méd., 1935, p. 729. (*e*) Nicole, R.: Arteriospasmus bei akuter Venenthrombosen, Schweiz. med. Wchnschr. **65**:676, 1935. (*f*) Gardère, H., and Desjacques, R.: Phlébite du membre inférieur simulant une embolie artérielle; diagnostique différentiel par l'acécoline, Presse méd. **45**:158, 1937. (*g*) Läwen, A.: Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, Arch. f. klin. Chir. **189**:53, 1937. (*h*) Läwen, A.: Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, Zentralbl. f. Chir. **64**:961, 1937; abstracted, ibid. **64**:1239, 1937. (*i*) Lindgren, S.: Arteriensymptome bei den tiefen Beinthrombosen, Upsala läkaref. förh. **42**:415, 1937. (*j*) Audier, M.: L'acétylcholine dans le traitement des phlébites des membres, Monde méd. **48**:17, 1938. (*k*) Chevrier, in discussion on Grégoire,[56l] p. 367. (*l*) Cornil, L., and Audier, M.: Les phlébartérites des membres, J. méd. franç. **27**:337, 1938. (*m*) Mondor, in discussion on Grégoire,[56l] p. 367. (*n*) Pampari, D.: Tromboflebite acuta degli arti e fenomeni pseudo-embolici, Policlinico (sez. chir.) **45**:470, 1938. (*o*) Pesnel, P.: À propos de spasmes des vaisseaux des membres inférieurs consécutifs à des affections veineuses, Semaine d. hôp. de Paris **14**:378, 1938. (*p*) dos Santos, J. C.: La phlébographie directe; conception; technique; premiers résultats, J. internat. de chir. **3**:625, 1938; (*q*) Spasme veineux du bras après injection intra-artérielle; action de l'infiltration du ganglion étoilé; contrôle phlébographique avant et après l'infiltration, Rev. de chir. **76**:308, 1938. (*r*) Uggeri, C., and Massone, A.: La sintomatologia arteriale delle flebiti degli arti, Arch. ital. di chir. **49**:429, 1938.

who showed that in the absence of pulsations there was almost no movement of lymph but that in the presence of pulsations the lymph flow was rapid. Monteiro [64] has shown also that blocking of the sympathetic nerves increases the flow of lymph. We [58] have shown experimentally and clinically that in the presence of a thrombophlebitic process the volume of peripheral arteriolar pulsation is considerably diminished and that in many instances the pulsation is almost imperceptible (fig. 3). This is due not only to the associated vasospasm but to increased venous pressure.[65] The decrease in lymph flow results in stagnation of tissue fluids and accumulation of proteins in the perivascular fluid, thus setting up a vicious circle in that the pressure of the perivascular fluid approaches that of the fluid within the vessel, tending to prevent resorption of fluid from the perivascular spaces into the vascular tree. Thus, it is evident that vasoconstrictor impulses originating in a thrombophlebitic process play a significant role in production of the clinical manifestations of thrombophlebitis. When the vasoconstrictor impulses are interrupted by infiltration of the sympathetic ganglions with procaine hydrochloride, there is produced a reestablishment of the normal exchange of intervascular and perivascular fluids and a breaking up of the vicious circle.

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60. (*a*) Bergeret, A.; Guillaume, A. C., and DeLarue, J.: Gangrène ischémique du membre inférieur par thrombose oblitérante de la totalité des veines, Ann. d'anat. path. **9**:536, 1932. (*b*) Wertheimer, P., and Frieh, P.: Thromboses veineuses, oblitérations artérielles et gangrène des membres; documents cliniques, Presse méd. **43**:1004, 1935. (*c*) Audier, M.: Thromboses veineuses aiguës simulant l'embolie artérielle des membres, Paris méd. **1**:384, 1936. (*d*) Fontaine, R.; Israel, L., and Pereira, S.: À propos d'un cas de thrombose de la veine cave inférieure. Thrombo-phlébites simulant les embolies artérielles et gangrènes d'origine veineuse, J. de chir. **47**:926, 1936. (*e*) Audier, M., and Haimovici, H.: Les gangrènes des membres d'origine veineuse, Presse méd. **46**:1403, 1938. (*f*) Banzet, P., in discussion on Grégoire,[59l] p. 367. (*g*) Grégoire, R.: La phlébite bleue (phlegmasia cærulae dolens), Presse méd. **46**:1313, 1938. Pallin.[59a] Trémolières and Veran.[59b] Läwen.[59c] Lindgren.[59i] Chevrier.[59k] Pampari.[59n]

61. Tilley, J. H.: Gangrene of Extremities in Thrombophlebitis, Am. J. Obst. & Gynec. **36**:157, 1938. Decoulx, P., and Bastien, P.: Gangrène par spasme artériel au cours d'une phlébite, Ann. d'anat. path. **16**:353, 1939. Bergeret and his associates.[60a] Fontaine and his associates.[60d] Audier and Haimovici.[60e]

62. McMaster, P. D., and Parsons, R. J.: The Effect of the Pulse on the Spread of Substances Through Tissues, J. Exper. Med. **68**:377, 1938. Parsons, R. J., and McMaster, P. D.: The Effect of the Pulse upon the Formation and Flow of Lymph, ibid. **68**:353, 1938.

63. Cressman, R. D., and Blalock, A.: The Effect of the Pulse upon the Flow of Lymph, Proc. Soc. Exper. Biol. & Med. **41**:140, 1939.

64. Monteiro, H.: La lymphangéiographie chez le vivant; Méthode, résultats et application, Bruxelles méd. **19**:205, 1938; La lymphangéiographie chez le vivant; méthode, résultats et application, ibid. **19**:242, 1939.

65. Burch, G. E.; DeBakey, M., and Sodeman, W.: Effect of Venous Pressure on Pulse Volume, Proc. Soc. Exper. Biol. & Med., to be published.

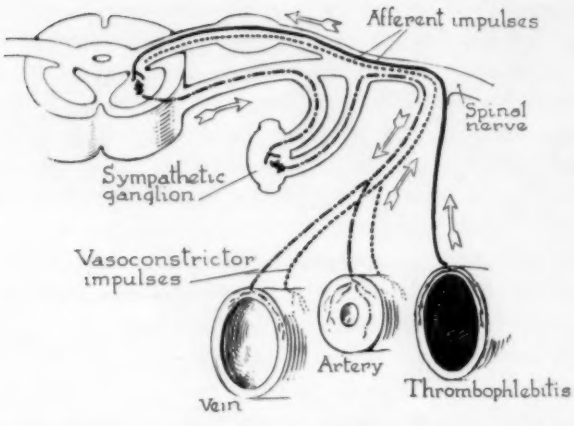

Fig. 1.—Diagrammatic representation of the mechanism of development of the clinical manifestations of thrombophlebitis. Impulses (depicted by arrow) originating in the thrombosed venous segment set up a vasomotor reflex resulting in generalized vasospasm of the involved extremity.

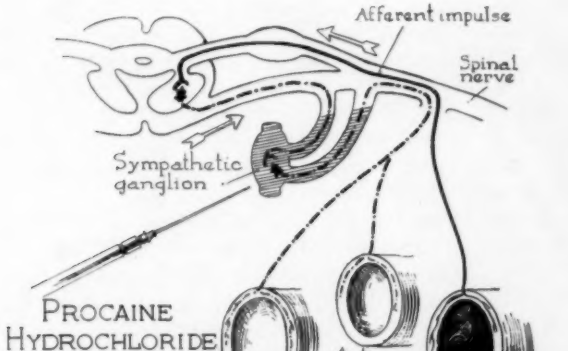

Fig. 2.—Diagrammatic representation of the mechanism of relief of the clinical manifestations after procaine hydrochloride block in cases of thrombophlebitis. Block of the sympathetic ganglions with procaine hydrochloride interrupts the vasoconstrictor impulses and results in breaking of the vasomotor reflex.

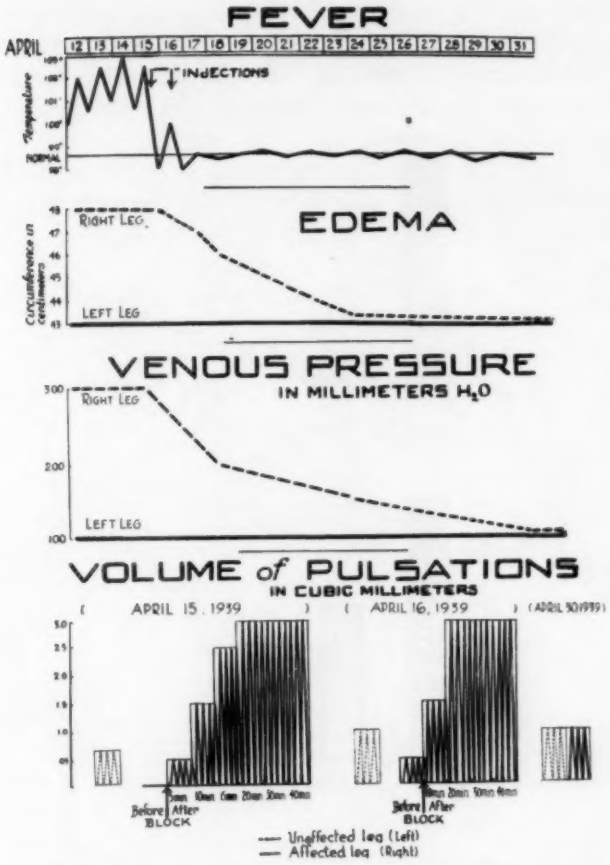

Fig. 3.—Graphic representation of the temperature, edema, venous pressure and volume of peripheral pulsations in a case of thrombophlebitis of the right lower extremity following cesarean section. The temperature ranged between 101 and 103 F. but dropped to normal and remained there within forty-eight hours after the first "lumbar sympathetic block" (indicated by arrows). All swelling of the extremity had completely subsided seven days after therapy was begun. The venous pressure (taken in the saphenous vein at the ankle at heart level), which was 300 mm. of water, rapidly dropped to less than 200 mm. within three days of the first block and was practically normal within two weeks. The peripheral pulsations as determined plethysmographically were normal in the unaffected leg (left) but were practically absent in the affected leg (right) before block, suggesting vasospasm. Within ten minutes after block of the sympathetic fibers on the right, the pulsations were twice the volume of pulsations in the normal (left) leg, showing release of vasoconstrictor impulses. Similar observations, although less marked, were made the following day. On the day before the patient was discharged, peripheral pulsations in the right and in the left toes were equal.

We have reported elsewhere [66] the results of this form of therapy for thrombophlebitic processes. Since then, similar measures have been used in 5 additional cases, with prompt and permanent relief of all clinical manifestations. Pain has been relieved within fifteen minutes to a half an hour after the first injection in 86.3 per cent of the cases

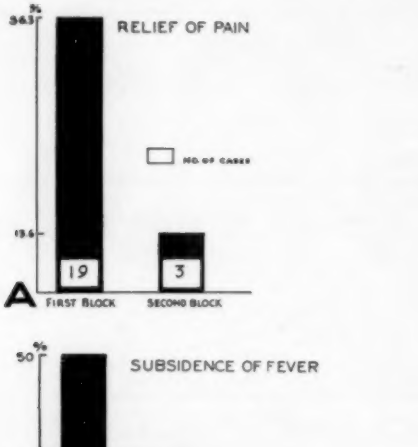

Fig. 4.—Graphic representation of (*A*) relief of pain, (*B*) subsidence of fever and (*C*) subsidence of edema after institution of "sympathetic block" with procaine hydrochloride in personally observed cases of thrombophlebitis.

and in the remainder after the second injection (fig. 4 *A*). Relief of pain was permanent. In no instance did the pain persist after the second

66. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, Surgery **5**:491, 1939. Ochsner, A.: Thrombophlebitis, ibid. **6**:129, 1939. Ochsner and DeBakey.[58b]

injection. Over half the patients were free from fever within forty-eight hours after institution of therapy (fig. 4 *B*). There were only 2 patients who had fever longer than one week, 1 for eight days and 1 for thirty-one days. The latter patient had a pulmonary infarct, although all of the thrombophlebitic manifestations of the extremity had completely subsided within nine days. This patient subsequently made a complete recovery. The subsidence of edema was unusually rapid. Eight patients showed complete subsidence of edema within four days. All but 2 of the patients had complete subsidence of edema within ten days, and in these 2 the edema had subsided on the eleventh and on the twelfth day respectively after institution of therapy (fig. 4 *C*). Two thirds of the patients were discharged from the hospital cured within eight days after institution of therapy and 90 per cent within twelve days (fig. 5). Only 2 patients remained longer, 1 because of a pulmonary infarct and the other to permit more extensive experimental studies. Of particular interest are the follow-up observations on a number of these patients observed over periods varying from four months to over a year. In none has there been any evidence of recurrence of edema or of other postphlebitic manifestations. No other form of therapy was used in these cases.

We have used this method in 2 cases of "effort thrombosis." This interesting thrombotic phenomenon has been exhaustively reviewed by Matas.[67] Others [68] have also described the severe clinical manifestations

67. Matas, R.: On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain: Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of the Lesion in Its Medico-Legal Relations, Am. J. Surg. **24:** 642, 1934.

68. Lowenstein, P. S.: Thrombosis of the Axillary Vein: An Anatomic Study, J. A. M. A. **82:**854 (March 15) 1924. Schwindt, J. K.: Traumatic Thrombosis of the Upper Extremity, California & West. Med. **27:**635, 1927. Gould, E. P., and Patey, D. H.: Primary Thrombosis of the Axillary Veins: Study of Eight Cases, Brit. J. Surg. **16:**208, 1928. Horton, B. T.: Primary Thrombosis of the Axillary Vein, J. A. M. A. **96:**2194 (June 27) 1931. Paggi, B.: Trombosi venose da sforzo degli arti superiori, Policlinico (sez. chir.) **40:**383, 1933. Taylor, C. H. S.: Primary Thrombosis of Subclavian Vein, Brit. M. J. **2:**818, 1933. Piccagli, G.: Trombosi da sforzo della vena ascellare destra, Chir. d. org. di movimento **19:**186, 1934. Ballon, H. C.: Primary Thrombosis of the Axillary Vein, Canad. M. A. J. **32:**414, 1935. Barker, N. W.: Axillary Thrombophlebitis Caused by Strain or Effort, Proc. Staff Meet., Mayo Clin. **10:**156, 1935. Veal, J. R., and McFetridge, E. M.: Primary Thrombosis of the Axillary Vein: An Anatomic and Roentgenologic Study of Certain Etiologic Factors and a Consideration of Venography as a Diagnostic Measure, Arch. Surg. **31:**271 (Aug.) 1935. Kaplan, T., and Katz, A.: Thrombosis of Axillary Vein: Case Report with Comments on Etiology, Pathology and Diagnosis, Am. J. Surg. **37:**326, 1937. Puhl, H.:

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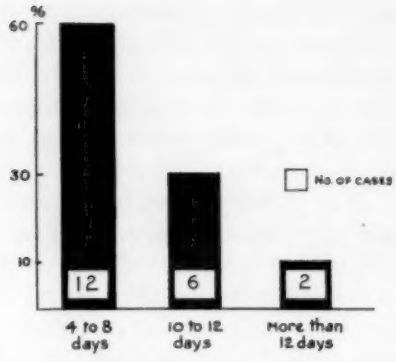

Fig. 5.—Graphic representation of the duration of hospitalization after institution of "sympathetic block" with procaine hydrochloride in personally observed cases of thrombophlebitis.

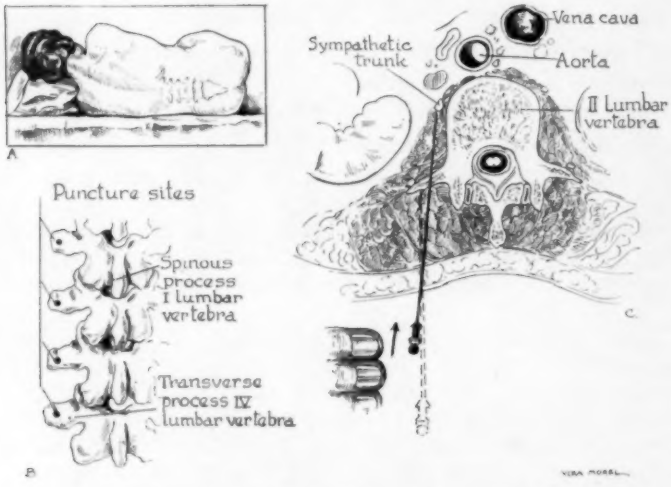

Fig. 6.—Diagrammatic illustration of the technic of "lumbar sympathetic block" for thrombophlebitis of the lower extremity. *A*, patient in the lateral recumbent position. *B*, cutaneous sites of puncture, lying immediately over the transverse processes of the vertebrae. They may be determined by taking points approximately 2½ fingerbreadths lateral to and on a horizontal level with the spinous processes of the first four lumbar vertebrae. *C*, insertion of the needles. Each needle is inserted vertically until the transverse process of the vertebra, as shown by the dotted needle, is reached. The direction of the needle is then changed slightly toward the midline, and the needle is inserted approximately 2½ fingerbreadths beyond the transverse process, so that its point lies near the anterolateral surface of the body of the vertebra, where the sympathetic chain lies. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected through each needle, care being taken to determine previously that the needle is not in a vessel.

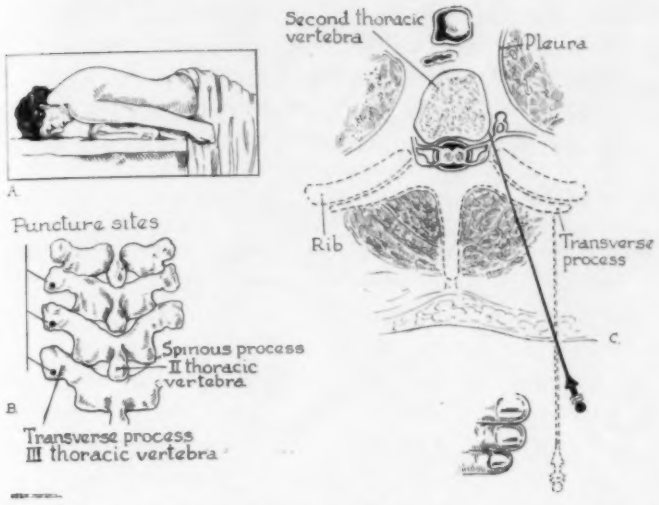

Fig. 7.—Diagrammatic illustration of the technic of cervicodorsal sympathectomy by the posterior approach. *A*, patient in the prone position with pillows beneath the chest. *B*, cutaneous sites of puncture, lying immediately over the transverse processes of the first, second and third thoracic vertebrae. They may be determined by taking points approximately 2½ fingerbreadths lateral to and on a horizontal level with the spinous processes of the seventh cervical and the first and second thoracic vertebrae. *C*, insertion of the needles. Each needle is inserted vertically until the transverse process, as shown by the dotted needle, is reached. The direction of the needle is then changed slightly toward the midline, and the needle is inserted 2½ fingerbreadths beyond the transverse process, so that the point of the needle is near the anterolateral surface of the body of the vertebra in the retropleural space, where the sympathetic chain lies. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected through each needle.

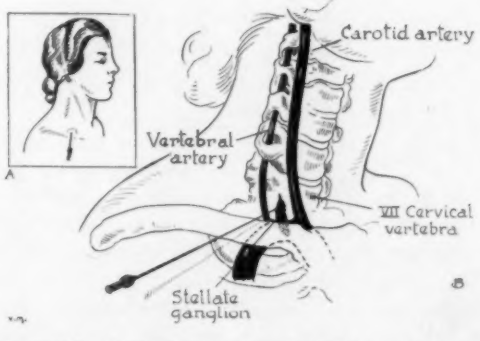

Fig. 8.—Diagrammatic illustration of the technic of block of the stellate ganglion by the anterior approach. *A*, patient's head turned slightly toward the opposite side. The cutaneous site of puncture is approximately 1 cm. medial to the midpoint of the clavicle and immediately over its upper border. *B*, insertion of the needle posteriorly and medially at an angle of 45 degrees with the midline and on a horizontal level with the upper border of the clavicle.

which are so characteristic of the condition. Our 2 patients treated by sympathetic block were rapidly and permanently relieved.

The technic of injection of the anesthetic into the lumbar sympathetic ganglions is relatively simple and has been described previously.[66] The technic employed by us is illustrated in figures 6, 7 and 8.

RADICAL THERAPY

Although the conservative measures are generally adequate, resort to more radical procedures may occasionally become necessary. This applies particularly to the suppurative type of thrombophlebitis, in which ligation of the vein above the involved process may prevent further extension. Ligation of the vein proximal to a thrombophlebitic area was first performed by Hunter[69] in 1784. The procedure was also done by Lee[70] in 1865. Ligation or excision of the pelvic veins in the treatment of septic thrombophlebitis of puerperal origin has been advocated by Bumm,[71] Sippel,[72] Trendelenburg[73] and numerous

Zur Frage der sogenannten Thrombose der Vena axillaris, Arch. f. klin. Chir. **190**:569, 1937. Tomasi, L.: Contributo alla patologia e alla clinica delle trombo-flebiti dell'arte superiore, Arch. ital. di chir. **43**:525, 1936; abstracted, Internat. Abstr. Surg. **64**:171, 1937. Andersson, O.: Venography in Case of So-Called Traumatic Thrombosis of Axillary Vein, Acta radiol. **19**:126, 1938. Kaplan, T.: Thrombosis of Axillary Vein: Report of Five Cases with Comments on Etiology, Pathology and Diagnosis, J. A. M. A. **110**:2059 (June 18) 1938. Mason, J. M.: Primary Thrombosis of Axillary Vein Caused by Strain, Internat. Clin. **1**:239, 1938. Wagner, W.: Beobachtungen und Behandlung bei der sogenannten Achsel-venenthrombose, Zentralbl. f. Chir. **65**:2169, 1938. Zschau, H.: Die sogenannte traumatische Thrombose der Vena axillaris und subclavia und ihre Begutachtung als Unfallfolge, München. med. Wchnschr. **85**:1990, 1938. Roelsen, E.: So-Called Traumatic Thrombosis of Axillary and Subclavian Veins, Acta med. Scandinav. **98**:589, 1939.

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71. Bumm, E.: Ueber die chirurgische Behandlung des Kindbettfiebers, Samml. zwangl. Abhandl. a. d. Geb. d. Frauenh. u. Geburtsh. **4**:1, 1902; Zur operativen Behandlung der puerperalen Pyämie, Klin. Wchnschr. **44**:829, 1905; Operative Behandlung des Puerperalfiebers, Zentralbl. f. Gynäk. **33**:962, 1909; Ueber die operative Behandlung des Puerperalfiebers, Verhandl. d. deutsch. Gesellsch. f. Gynäk. **13**:105, 1909.

72. Sippel, A.: Die operative Behandlung der puerperalen Pyaemie, Zentralbl. f. Gynäk. **26**:1361, 1902.

73. Trendelenburg, F.: A Review of Surgical Progress, J. A. M. A. **47**:81 (July 14) 1906; Ueber die chirurgische Behandlung der puerperalen Pyaemie, München. med. Wchnschr. **49**:513, 1902.

others.[74] Briggs[75] advocated ligation of the saphenous vein in cases of recurrent phlebitis to prevent embolism, and Pool and McGowan[76] reported a case of femoral thrombophlebitis successfully treated by ligation of the femoral veins. Proximal ligation with or without excision has been suggested by numerous others.[77] We have recently observed 1 case in which treatment by this means was successful. The patient was a white man 59 years of age who was admitted to the hospital complaining chiefly of pain and swelling in the left leg which began after an injury to the leg in an automobile accident. The traumatic thrombophlebitis of the popliteal vein responded readily to conservative therapy for approximately a week, after which the pain and swelling rapidly became worse, the patient had chills and the temperature rose to 104.8 F. The chills and hyperpyrexia recurred at six hour intervals, and the general condition of the patient appeared critical. Apparently a suppurative process had developed on the basis of the previous popliteal thrombosis, with production of recurrent septic emboli due to liquefaction

74. Lenhartz, H.: Acht Fälle von operierter puerperaler septischer Thrombophlebitis, Deutsche med. Wchnschr. **32**:817, 1906. Seitz, L.: Zur chirurgischen Behandlung der puerperalen Pyaemie, München. med. Wchnschr. **53**:2585, 1906. Williams, J. W.: Ligation of Excision of Thombosed Veins in the Treatment of Puerperal Pyaemia, Am. J. Obst. **59**:758, 1909. Miller, C. J.: The Present Status of Ligation or Excision of the Pelvic Veins in the Treatment of Septic Thrombophlebitis of Puerperal Origin, J. A. M. A. **59**:157 (July 20) 1912. Miller, C. J.: Ligation or Excision of the Pelvic Veins in the Treatment of Puerperal Pyaemia, Surg., Gynec. & Obst. **25**:431, 1917. Rosenstein, P.: Die Phlebektomie (operative Ausschaltung der fortschreitenden Thrombophlebitis), Arch. f. klin. Med. **109**:394, 1917. Kriele, J.: Frühzeitige Diagnose und Prognose der Pyämie, Ztschr. f. Geburtsh. u. Gynäk. **99**:35, 1930.

75. Briggs, J. B.: Recurring Phlebitis of Obscure Origin, Bull. Johns Hopkins Hosp. **16**:228, 1905.

76. Pool, E. H., and McGowan, F. J., Jr.: Septic Thrombophlebitis of Femoral Vein: Operative Treatment, Arch. Surg. **8**:763 (May) 1924.

77. Läwen, A.: Ueber die Rolle der Venen bei der Ausbreitung pyogener Prozesse, Chirurg **1**:682, 1929. Homans, J.: Thrombophlebitis of the Lower Extremities, Ann. Surg. **87**:641, 1928. Dreyfuss, W.: Die Phlebektomie als Behandlungsmethode der Thrombophlebitis und ihre Komplikationen, Deutsche Ztschr. f. Chir. **217**:321, 1929. von Rehren, W.: Ueber einen Fall von geheilter Extremitätenpyämie durch Unterbindung der Vena iliaca communis sinistra, Zentralbl. f. Chir. **58**:1426, 1931. Stone, H. B.: Surgical Treatment of Post-Operative Saphenous Thrombophlebitis, Ann. Surg. **96**:683, 1932. Neuhof, H.: The Diagnosis and Operative Control of Acute Pyogenic Phlebitis Complicated by General Septic Invasion, ibid. **97**:808, 1933; Excision of Vein for Suppurative Thrombophlebitis, ibid. **106**:311, 1937. Ranzi, E., and Huber, P.: Postoperative Thrombose und Embolie, Wien. klin. Wchnschr. **48**:289, 1935. Bancroft, F. W.: Proximal Ligation and Excision of Veins for Septic Phlebitis, Ann. Surg. **106**: 308, 1937. Sears, J. B.: Embolism from Saphenous Thrombophlebitis and Its Prophylaxis, New England J. Med. **212**:874, 1935.

and breaking off of the infected clot. Approximately forty-eight hours after the onset of the septic manifestations the femoral and saphenous veins were exposed with the region under local procaine hydrochloride analgesia, and the saphenous vein was ligated just proximal to the saphenofemoral junction. After this, a block of the lumbar portion of the sympathetic nervous system was performed as has been described. Immediately after this, the pain and tenderness in the extremity were completely and permanently relieved. Within twelve hours the temperature returned to normal and remained normal (fig. 9). The leg became warm, dry and pink, and in four days all swelling in it had subsided. The patient was discharged two days later.

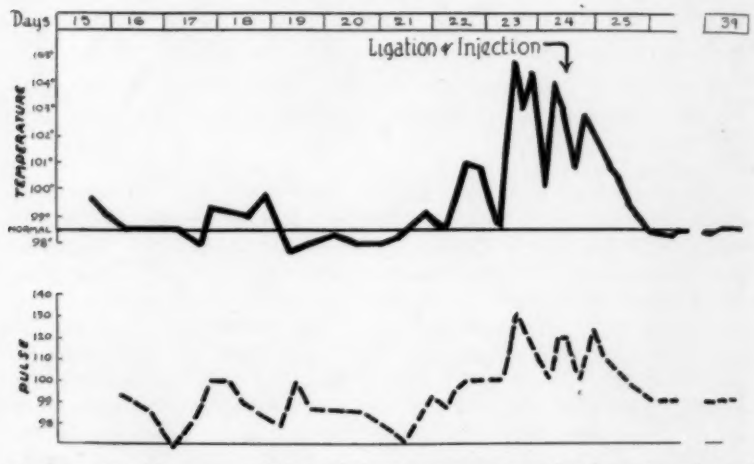

Fig. 9.—Graphic representation of the temperatures and pulse rates of a patient with septic thrombophlebitis. Ligation of the femoral vein and procaine hydrochloride block of the regional sympathetic nerves were performed.

Embolectomy (or thrombectomy) has also been suggested. Demons,[78] in 1881, reported its successful use in a case of suppurative thrombophlebitis of the median basilic and cephalic veins. Büdinger[79] also advocated the procedure. Läwen[80] has repeatedly emphasized the significance of thrombectomy. It is his opinion that removal of the thrombus is of value not only because it prevents the occurrence of

78. Demons: Contributions au traitement antiseptique des phlébites, Bull. et mém. Soc. de chir. de Paris **7**:878, 1881.

79. Büdinger, K.: Operativen Behandlung der akuten zirkunskriften Phlebitis, Wien. klin. Wchnschr. **25**:1217, 1912.

80. Läwen, A.: Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, Arch. f. klin. Chir. **189**:53, 1937; Weitere Erfahrungen über operative Thrombenentfernung bei Venenthrombose, ibid. **193**:723, 1938; abstracted, Zentralbl. f. Chir. **65**:1257, 1938.

emboli but because the presence of a thrombus in a venous segment acts as a focus for production of reflex vasospasm in that extremity. He has reported excellent results from this procedure. Kulenkampff [81] has recently reported 61 cases and stated that after removal of the thrombus the saphenous vein should be ligated close to the femoral vein.

SUMMARY

The therapy of thrombophlebitis is reviewed and is classified into prophylactic, conservative and radical measures.

The prophylactic measures consist of hydration, mobilization, respiratory stimulation, prevention of increased abdominal tension, application of heat, administration of sodium thiosulfate, hirudinization and heparinization.

The conservative measures consist of immobilization and elevation of the involved extremity, application of heat, hirudinization, use of compression bandages and production of vasodilatation.

In the authors' experience the best therapeutic measure is procaine hydrochloride block of the regional sympathetic nerves. The rationale of this therapeutic measure is discussed, and the excellent results obtained from its employment in 22 cases are described. The technic of "sympathetic block" as used by the authors is briefly described and illustrated.

The radical procedures consist of ligation, excision, incision and drainage and thrombectomy or embolectomy.

81. Kulenkampff, D.: Die Verhütung schwerer oder tödlicher Embolien durch Ausräumung der Vena iliaca, Arch. f. klin. Chir. **193**:727, 1938; abstracted, Zentralbl. f. Chir. **65**:1258, 1938.

LYMPHEDEMA OF THE LIMBS

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The states described here are those characterized by failure of the lymphatics to fulfil their function of draining the tissues of fluid which the blood capillaries are unable to accept. This failure may be due to an inherent defect in the lymphatic system, to an acquired organic blockage or to a disorder, once functional, which has become organic. Excluded from consideration are the nutritional edemas, the nephritic edemas, the cardiac edemas and the edemas of pregnancy; in short, all that are related to general or constitutional, as opposed to local, causes.

The tissue fluid is of course derived from blood. Such of it as is composed of water and salts reenters the blood capillaries, but plasma proteins and foreign material are unable to do so. Material of this sort and, in general, all substances whose contact with the body cells might harm the organism must, then, be carried off by the lymphatics. Just how such material, especially particulate matter, enters the lymphatics is not entirely clear and is not material here.

The ultimate lymph channels constitute a closed system, endothelium lined, which gathers itself into many tiny valved vessels capable of carrying lymph only toward the vena cava. These, following in the superficial tissues the general direction of the veins and in deeper parts circling about the great vessels, are gathered together at the root of the various limbs, where they pass, on their way to the thoracic duct, through great groups of lymph nodes. Exercise causes lymph to flow rapidly and abundantly, but in a flaccid limb it accumulates. Indeed, it behaves much like blood within the veins; it must be squeezed or pumped out of the limbs and in default of movement swelling occurs. Should venous pressure be raised, there is at first an increased flow of normal lymph, but as the pressure is elevated more and more, the lymph changes in character, becoming highly proteinized and even containing red blood cells.

It must, then, be clear that lymphedema may result from many causes. Three principal groups are readily recognizable:

1. A group of edemas associated with disuse and injury and due primarily to failure of the lymphatics to dispose of tissue fluids normally produced.

2. A group of edemas associated with venous obstruction and due primarily to failure of the lymphatics to dispose of an excess of tissue fluids forced on them by elevated venous pressure.

3. A group of edemas due to a natural or acquired deficiency of the lymphatics themselves, that is, elephantiasis.

To these groups should be added several which are less well understood. Perhaps they are not lymphedemas in the ordinary sense, but

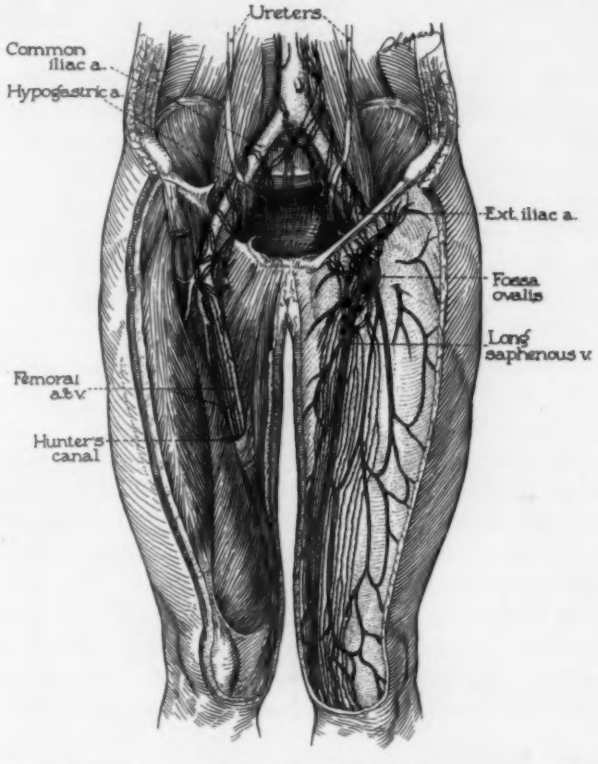

Fig. 1.—Lymphatics of the legs. In the left leg, some of the superficial lymphatics, which lie in the same plane with the superficial veins, are shown. These join the deep (perivascular) lymphatics at the groin. In the right leg, the deep lymphatics, which drain the back of the leg and foot, are represented. Rouvière's descriptions have in the main been followed.

they are confusable with them and must be identified and treated by special methods. Such are:

4. A group of reflex, or "trophic," edemas, related to countless causes and including the causalgia-like states.

5. A group of allergic edemas, due to hypersensitiveness to foreign substances, especially the fungi of the skin.

6. Cavernous lymphangiomas.

The lymphedemas, or, if one prefers, swellings, peculiar to the limbs will be considered here in the order just outlined and under the following headings: (1) edemas directly due to disuse and injury; (2) edemas due to venous thromboses; (3) elephantiasis; (4) reflex edemas; (5) allergic edemas, and (6) cavernous lymphangiomas.[1]

EDEMAS DUE TO DISUSE AND INJURY

Since the borderline between swelling and no swelling in a limb is narrow, edema due to the muscular atrophy which results from confinement to bed is very common. After even a few weeks in bed, and all the more after many months, some persons notice swelling of the ankles on first getting about. Since it is the pumping mechanism which is deficient, the edema quickly disappears on elevation of the limb. It disappears overnight and returns during the day until such time as the muscles regain their tone and the patient his normal activity. This sort of edema should be kept in mind, because it may be confused with the onset of a late and quiet phlegmasia alba dolens, from which it is distinguished by its daily development and nightly disappearance and by the absence of any discomfort.

A similar edema is associated with the late effect of sprains and fractures, that is, those which leave stiff joints and atrophied muscles. It may even be noticed in some persons who have badly pronated feet which they use ineffectively, and it is common in aged persons, inactive, who do much standing about.

In all such states the swelling disappears on a night's rest in bed. It is very different from the acute edema of a sprain, which is either an exudate or, as Leriche would have one believe, a result of a sympathetic dysfunction due to trauma (as such it will be discussed with the reflex edemas).

EDEMAS DUE TO VENOUS THROMBOSIS

During the active stage of any deep thrombophlebitis, that is the femoroiliac form or the form involving the lower part of the leg, there usually is marked edema (by contrast with thrombosis in the superficial veins, which rarely causes any swelling). Such edema can partly be explained as due to elevated venous pressure, the lymphatics being normal but unable to carry off the enormous transudate of tissue fluid. But this is not the whole story. In many instances of femoroiliac

1. Cystic lymphangiomas, almost peculiar to the root of the neck, are entirely different from the lymphedemas of the limbs and are not included here.

thrombophlebitis there is present about the great artery and vein in the groin and along the pelvic brim an active inflammatory exudate which covers everything in the vicinity. It undoubtedly engulfs the principal lymph trunks, which course about great blood vessels, and so may add lymphatic obstruction to the excessive edema caused by the venous stasis. How much edema results from this cause is difficult to say. By some it is regarded as of great importance. Others belittle it and attribute such edema as is not due to elevated venous pressure to reflex vasospasm occasioned by irritation of the plexus of nerves which surrounds the thrombosed vein and its companion artery. That a peripheral vasospasm is often associated with femoroiliac thrombophlebitis and actually occasions edema or at least prevents its relief is attested by Leriche's [2] treatment of this disease by procaine block of the lumbar portion of the sympathetic nervous system. He asserts, and Ochsner and DeBakey [3] confirm his observations, that such an injection, repeated over a number of days, relieves discomfort and causes the edema rapidly to disappear.

It must, then, be supposed that the most serious swelling of the lower limb [4] is due to the edema of combined venous and lymphatic obstruction reenforced by peripheral vasospasm. Such a swelling is occasionally remarkably persistent (fig. 2 *A*). If a collateral venous circulation is slow to develop and if the lymphatics are unusually crippled, it may remain present in some degree for months or years or even throughout life. Its tendency, however, is to diminish with time, especially if the disease has been treated from the beginning by elevation of the swollen limb above the body and by measures capable of relieving such peripheral spasm as may be present. It is particularly important that during the gradual resumption of active use the leg should be protected by elastic pressure. Prolonged lymph stasis leads to fibrosis and to further crippling of the drainage system, a vicious circle. Moreover, in rare instances a causalgia-like state, marked by cyanosis, edema and perhaps a hypersensitive skin, may set in (fig. 2 *B*). Under these conditions, a lumbar sympathetic block with procaine hydrochloride temporarily relieves hypersensitiveness and restores a natural color to the foot. Whether lumbar sympathectomy will then be curative or, as Leriche [2]

2. Leriche, R.: The Problem of Osteo-Articular Diseases of Vasomotor Origin: Hydrarthrosis and Traumatic Arthritis; Genesis and Treatment, J. Bone & Joint Surg. **10**:492 (July) 1928.

3. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics: Technique of Injection, Surgery **5**:491 (April) 1939.

4. This account leaves out of consideration the rare reflex spasm of the iliac and femoral artery itself, a spasm which altogether shuts off the arterial supply to the limb and so, if continued, leads to gangrene. But in such a case edema is altogether absent.

believes, the great iliac veins must, in addition, be freed from scar tissue and perhaps divided, is not yet clear.

Serious phlegmasia alba dolens is followed in many instances by peculiar local indurations and ulcerations of the lower part of the leg (postphlebitic induration and ulceration). Such appear months or

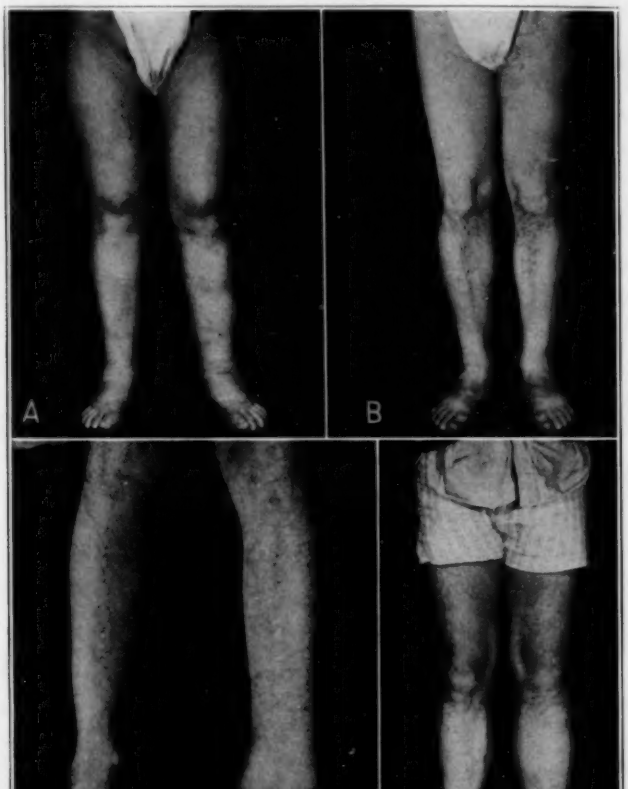

Fig. 2.—*A*, legs of M. C. S. There is postphlebitic bilateral edema with a possible allergic factor. *B*, legs of J. B. T. There is postphlebitic edema of the right leg with causalgia-like hypersensitiveness. The cyanotic color of the foot is missed in the photograph. *C*, traumatic, reflex edema excited by the fall of a block of wood on the foot, subsequently cured by lumbar sympathectomy. An allergic factor related to fungi may have been present. (From Homans, J.: Circulatory Diseases of the Extremities, New York, The Macmillan Company, 1939). *D*, legs of A. J. D. Allergic edema related to fungi was present. The condition was successfully treated by lumbar sympathectomy.

years after the original disease and have usually been mistaken for complications of varicosity, which fundamentally they are not. But that they are actually the result of lymph stasis is not clear either, and in many instances they certainly are aggravated, if not actually excited, by fungous infection. Treatment of such infection aids in their cure, and sympathectomy influences them favorably, but when especially obstinate and extensive they must be treated by excision and skin graft.

The moderate edema occasioned by thrombosis in the great venous plexuses among the muscles of the calf is peculiar. It is confined to the lower part of the leg and when the patient is up and about is associated with some degree of cyanosis. Several days of elevation of the limb in bed causes it to disappear completely, but it returns on the resumption of an active life. I have elsewhere described this disease, which is distinguished by the alternations just described and by a sense of discomfort in the back of the upper part of the calf on forced dorsiflexion of the foot. Owing to the tendency of the thrombosis to grow into the femoral vein as a loose, propagating clot, it is a frequent source of fatal pulmonary embolism.

ELEPHANTIASIS

According to the manner in which elephantiasic edema makes its appearance, there are several varieties. In none of them, however, is the means by which lymphatic drainage is abolished at all well understood. Operative intervention introduces the surgical sort; filarial infection usually brings on the tropical sort, but the cause of the sporadic and familial varieties is utterly obscure. The end results of all are much the same. The lymphatic system of the elephantiasic limb is entirely destroyed; that is, no valved lymphatics are left and fluid drifts through the interstices of the subcutaneous tissues, some of which may present the appearance of dilated lymph spaces, by gravity alone. No lymph nodes are seen.

In the tissues superficial to the muscular aponeurosis the retained tissue fluid acquires, as the years go on, a large percentage of protein, a proportion sometimes so high as to be more than half that of blood serum—4 per cent in exceptional cases. Probably this proteinized fluid acts as a tissue culture medium and encourages fibrosis. In any event, the tissues become steadily firmer and the skin coarser, thicker and often hairy. Some limbs preserve their shape, though there is usually sagging of the skin over the line of the shoe, but in others the skin gives way here and there, forming bizarre deformities, great folds and pouches. From any scratch or prick a clear, pale yellow fluid runs freely until the scratch heals. Healing, in fact, in such limbs is usually normal, the blood supply being abundant.

The tissues beneath the aponeurosis, that is, the muscles, remain entirely unchanged, a sign that the muscles themselves are not drained

by lymphatics but by capillaries alone. The elephantiasic leg is, of course, unwieldy, yet seems to suffer no muscular deterioration. However, there is no support for Kondoléon's [5] plan of introducing the fluids of the superficial tissues among the muscles. Even if that could be done, it would presumably embarrass the muscles without improving drainage.

The febrile attacks to which the elephantiasic limb is subject are more common in tropical countries than elsewhere but may set in, without apparent reason, in the sporadic elephantiasis of temperate climates. After a preliminary period of discomfort, which in the filarial form of the disease is often marked by localized pain and tenderness, the entire limb becomes swollen and its surface red and hot. A chill is rather common, after which the temperature rises rapidly to 102 or 104 F. and the patient is greatly prostrated. Indeed, the illness may appear dangerous, but actually the attack is self limited, subsiding in three to five days. Though it has often been supposed that the infection is streptococcic—it should never be called "lymphangitis," since there are no lymphatics left—Drinker and Field were the first to prove it to be such in the experimental animal. Actually, in their observations the attacks started automatically, and the streptococci could be recovered for only a few hours near the height of the attack. This explains the difficulty of finding the causative organisms in human beings. A brief account of these experiments is included in papers on the general subject of elephantiasis by Drinker, Field and me.[7]

The fungi of the skin may also be concerned with these explosions, though perhaps only indirectly. For example, an active young man suffering from elephantiasis with attacks so frequent and severe that he had become an invalid was so far relieved by a plastic operation that for two years he remained well. Finally, however, during hot, damp summer weather, an old epidermophytosis recurred, and a bad attack of elephantiasis followed. Probably streptococci entered the tissues, as they so often do, via the cutaneous lesion, though it is conceivable that the attack was allergic. Vigorous treatment subdued the epidermophytosis, and the trouble has not been repeated.

Surgical Elephantiasis.—This form affects most often the arm, following operations for cancer of the breast. It may occasionally

5. Kondoléon, E.: Die operative Behandlung der elephantiastischen Oedeme, Zentralbl. f. Chir. **39**:1022, 1912.

6. Footnote deleted.

7. Homans, J.; Drinker, C. K., and Field, M. E.: Elephantiasis and the Clinical Implications of Its Experimental Reproduction in Animals, Ann. Surg. **100**: 812 (Oct.) 1934. Drinker, C. K.; Field, M. E., and Homans, J.: The Experimental Production of Edema and Elephantiasis as a Result of Lymphatic Obstruction, Am. J. Physiol. **108**:509 (June) 1934.

appear as a late complication of malignant disease in the pelvis, whether treated by operation or by irradiation. It may also result from lymphosarcoma in the groin or axilla, especially when an operation has been performed and the part subjected to irradiation.

Elephantiasis of the arm as a complication of mammary cancer occurs in a very freakish way. An axillary dissection alone, in the event of a mistaken diagnosis of cancer, is capable of producing it, though not in the serious form due to axillary metastasis plus operation and recurrence.

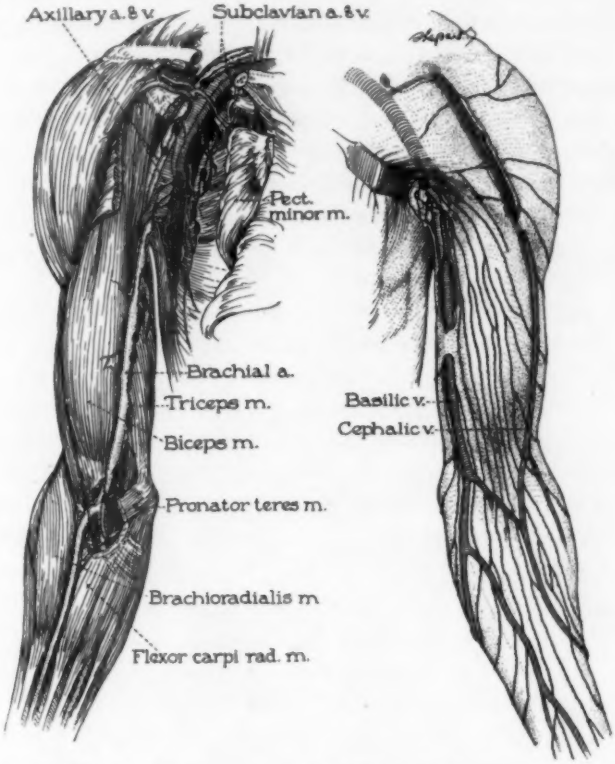

Fig. 3.—Lymphatics of the arms. In the left arm, some of the superficial lymphatics are shown. They enter the axilla with the basilic vein. In the right arm, the deep (perivascular) lymphatics of the forearm, arm and axilla are represented. They are closely related, as in the leg, to the artery rather than to the vein. Rouvière's descriptions have in the main been followed.

Recently, Veal [8] has found that there are a pure lymphatic variety, a sort due to venous obstruction and a mixed type. So far as the lymphatics are concerned, it will be recalled that most of the small vessels

8. Veal, J. R.: The Pathological Basis for Swelling of the Arm Following Radical Amputation of the Breast, Surg., Gynec. & Obst. **67**:752 (Dec.) 1938.

of the skin and subcutaneous tissues of the hand and arm come together and enter the axilla at the spot where the basilic vein perforates the aponeurosis. Here they can readily be interrupted, but after entering the axilla they are more closely related to the axillary artery than to the vein. Thus they are not particularly exposed in the axillary dissection proper. Moreover, a variable amount of lymphatic drainage passes through the lymph nodes at the elbow and so along the brachial and axillary arteries. Thus, an axillary dissection may well leave the lymph drainage system intact unless most of the superficial vessels are divided in making the skin flap or unless axillary metastasis is extensive.

In some cases, evidence that the axillary dissection has interrupted many lymphatics is offered immediately after operation by a collection of clear lymph in the wound. Even then the fluid often finds a way. Swelling may occasionally appear and disappear, or perhaps remain moderate, a matter explainable on anatomic grounds. However, once well marked surgical lymphedema sets in, typical elephantiasis usually develops, with the characteristic induration and thickened skin and even the febrile attacks.

The treatment of surgical elephantiasis is, first and foremost, elevation of the part. The arm should be kept horizontal or raised on a pillow when not in use. It is even possible to devise means of suspending it at night. Exercise, in moderation, is rather good for it than otherwise. In fact, fluid can escape from the arm only by gravity or by being forced through the tissue spaces. Plastic operations are difficult and unsatisfactory. For the most fully developed sort, amputation is the best remedy, provided the patient has a moderate life expectancy.

Filarial Elephantiasis.—Not all persons having filarial infestation suffer from elephantiasis. Indeed, O'Connor, Golden and Auchincloss,[9] with the aid of the roentgen rays, have demonstrated numbers of calcified worms in the tissues in the absence of any edema. But once the lymphatics are crippled, the tropical disease is more serious than that of temperate regions, because, as Matas[10] has pointed out, the patient is exposed to so many infections. Febrile attacks are common, and doubtless the tissues often permanently harbor bacteria which make surgical treatment difficult. Auchincloss[11] has attempted to excise as much infested

9. O'Connor, F. W.; Golden, R., and Auchincloss, H.: Roentgen Demonstration of Calcified Filaria Bancrofti in Human Tissues, Am. J. Roentgenol. **23**:494 (May) 1930.

10. Matas, R.: The Surgical Treatment of Elephantiasis and Elephantoid States Dependent upon Chronic Obstruction of the Lymphatic and Venous Channels, Am. J. Trop. Dis. **1**:60, 1913.

11. Auchincloss, H.: A New Operation for Elephantiasis, Porto Rico J. Pub. Health & Trop. Med. **6**:149 (Dec.) 1930.

subcutaneous tissue as possible, with the idea of removing focal spots whence outbursts of infection may come. However, the real value of such a procedure probably lies in the removal of a large amount of fluid-holding unhealthy tissue between the skin and the deep structures of the leg, and the modern operation is based on this general plan rather than on any idea of drainage. Such treatment is described in the following section.

Elephantiasis Nostra and Milroy's Disease.—Sporadic elephantiasis (elephantiasis nostra) is the rather common form which crops out here and there without known cause. Its nature and behavior differ in no way from those of the familial sort, to which Milroy's [12a] name is usually attached. Strangely enough, the family which formed the object of Milroy's [12b] study suffered from a disorder not only inherited but congenital; that is, almost all the members were affected in infancy. Meige [13] described a family in which the disease usually developed, as does the sporadic form, near puberty or soon after. Hope and French [14] have discovered another instance of this sort.

The cause of sporadic and familial elephantiasis is utterly unknown. Why should a person whose legs from birth to the age of 15 or 20 have seemed entirely normal, at that time and without suffering any accident or other physical change, begin to notice a swelling of one or both legs? I [15] have explored the pelvis in several patients, hoping to find an obstruction in the large lymph vessels which wind about the great artery and vein of the pelvic brim. In 1 case the lymphatics were thickened and enlarged but not dilated. They carried almost no lymph (probably a little from purely pelvic sources), and the nodes in their course were curious little flattened structures. In the tissues of the elephantiasic leg it is impossible to find anything like a valved vessel, though plenty of large spaces are present; and if a little trypan blue, a dye readily taken up by the lymphatics, is injected deep into the skin it either remains stationary or, if the leg is elevated, can be seen to color the skin in a patchy way, spreading about by gravity. It may flow from ankle to knee in as little as fifteen minutes, but this occurs only if there are unusually abundant cutaneous spaces. In fact, the tissue fluids flow up or down according as the leg is elevated or depressed but, having reached the body, appear to be rapidly absorbed.

12. Milroy, W. F.: (*a*) An Undescribed Variety of Hereditary Oedema, New York M. J. **56**:505 (Nov. 5) 1892. (*b*) Chronic Hereditary Edema: Milroy's Disease, J. A. M. A. **91**:1172 (Oct. 20) 1928.

13. Meige, H.: Dystrophie oedémateuse héréditaire, Presse méd. **6**:341 (Dec. 14) 1898.

14. Hope, W. B., and French, H.: Persistent Hereditary Oedema of the Legs with Acute Exacerbations, Quart. J. Med. **1**:312 (April) 1908.

15. Homans, J.: The Treatment of Elephantiasis of the Legs, New England J. Med. **215**:1099 (Dec. 10) 1936.

The general account of elephantiasis already given sufficiently fits the behavior of this particular disease. Both legs are enlarged in a fair number of cases, and in that event the external genitals as well may be involved. There is really no limit to the amount of enlargement or deformity, but evidently the tissues drain better in some instances than in others, so that certain elephantiasic legs never attain great size. The febrile attacks seem to occur only in the cases of more serious involvement, but actually their onset is unpredictable.

Treatment.—Palliative measures are not to be despised. Should the tissue fluids drain from the leg rather rapidly when it is elevated, a balance may be found between rest and use—so many hours up and so many down. The shoe prevents enlargement of that part of the foot which it covers, and an elastic stocking worn from toes to knee may, with the aid of exercise and elevation, permit a good deal of dependency. At night the foot of the bed should be raised, perhaps 6 inches (15 cm.), for it is during the sleeping hours that the best drainage is secured. By such means an occasional patient is able to control the disease.

The plastic operation aims, frankly, to do nothing more than remove the tissues in which fluid accumulates. By turning back broad flaps which include the aponeurosis and exposing bone, muscle and tendon sheaths, half the circumference of these deep structures can be laid bare at one sitting. Then the lymph-soaked fibrous tissue and sclerosed fat are cut from the deep surface of the flaps, which are left very thin. Indeed, it is probably best that these for two thirds of their width should be made of whole skin alone, a little fat being left near the base for purposes of venous drainage.[16] The incision for the first stage of the plastic operation is best made on the anterointernal face of the leg (fig. 4). Near the knee it becomes a broad Y, and at the internal malleolus, an unequal, inverted Y with a long arm forward. The difficulty with the blood supply of the flaps is not arterial but venous; that is, they receive enough blood but drain badly, and it is worth while to spare as many perforating veins as possible toward the base of each flap. Perhaps those who are accustomed to dealing with whole thickness skin grafts would do better to use these instead of flaps. However, if one scores the skin just before closing and makes firm, even, elastic pressure, very little sloughing occurs.

Each operation is carried out in a bloodless field by the aid of an Esmarch bandage applied to the thigh and reenforced if necessary with

16. A very interesting suggestion has recently been made to me by Dr. R. H. Smithwick, namely, that after a lumbar sympathectomy has been performed the flaps should be made of whole skin alone for their entire width. Dr. Smithwick reports that he has tried this procedure with success.

rubber tubing. Otherwise the operation is hopelessly bloody, and needless to say, the control of bleeding after the removal of the constricting rubber bandage is no easy matter. The only nerve which seems worth sparing is the sural, since this supplies the outer side of the foot and

Fig. 4.—Legs of M. A. B., a patient with elephantiasis nostra. The lower photographs illustrate successively, from left to right, the immediate result of the first plastic operation, the immediate result of the second plastic operation and the end result (at this time the patient was wearing an elastic stocking).

heel. Curiously enough, patients do not seem to object to the numbness of the leg. There is no danger of disturbing the nerve supply of the sole, toes and much of the foot.

The plastic operation which treats the second half of the leg must, of course, be postponed for several months after the first operation; otherwise the last two flaps could hardly be left back to back with the first ones. It will be observed that the foot, so far as it requires treatment, is fairly well reduced in size by the procedures described, but some thickened tissue is apt to be left in the midline from instep to toes. If necessary, this can be removed at a third operation, and any broad or hypertrophied scars, if such are present, can also be excised. At this time skin grafts may be useful, especially if infection or unsatisfactory healing is feared.

In cases of very serious involvement, when the sacculated parts are ulcerated and presumably infected, the plastic operations just described are not appropriate. Flaps made under these conditions are likely to slough, and infection is implanted on the hitherto uninvolved deeper parts. It will therefore be safest to excise great masses of tissue, including the underlying aponeurosis, without any flap making whatever. Then, after antiseptics have been applied for ten days or so, the clean, newly granulated surface can be covered with an Ollier-Thiersch or even a full thickness skin graft. I have recently carried out such a procedure successfully in the case of a man whose huge, deformed leg, the scene of innumerable febrile attacks, had worn him down and made an invalid of him (fig. 5).

REFLEX EDEMAS

These states are variously known as trophic edema and traumatic edema. They are related to causalgia and indeed are usually associated with so much hypersensitiveness of the skin as to deserve that name. They range from the terrible state of hypersensitive skin and burning pain described by Mitchell and his co-workers,[17] in which edema is trifling, to great swellings of a limb in which pain and sensitiveness to touch are perhaps little marked. It is proposed here not to discuss causalgia or the entire subject of the post-traumatic pain syndrome but to indicate how the traumatic edemas can be recognized.

Actually, reflex edema probably represents a dysfunction of the nervous mechanism associated with the blood vessels. The little nerves of this mechanism—whether they are purely vasomotor and therefore sympathetic or are sensory and therefore belong to the somatic nervous system—are carried on the blood vessels into the great nerve trunks, and so injuries of nerves as well as of blood vessels may throw

17. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W.: Gunshot Wounds and Other Injuries of Nerves, Philadelphia, J. B. Lippincott Company, 1864. Mitchell, S. W.: On a Rare Vasomotor Neurosis of the Extremities, and on the Maladies with Which It May Be Confounded, Am. J. M. Sc. **76**:17 (July) 1878.

them into disorder. Strangely enough, any one of a great variety of traumas, in the broad sense, may be the exciting factor. A block of wood falls on the foot (fig. 2*C*), a wound by a thorn or by the bite of an animal becomes mildly infected, femoroiliac thrombosis occurs

Fig. 5.—Photographs in the case of H. F. W., a patient with advanced elephantiasis nostra. There were disabling febrile attacks. The tissues were permanently infected. The whole back of the leg, the seat of a great local enlargement, was cut away. The subaponeurotic area exposed by the excision was covered with a thick Ollier-Thiersch graft. The attacks have been controlled, but further plastic procedures will be required.

(fig. 2*B*) or a Colles fracture or its reduction injures a median nerve; then the foot or the hand, the whole leg or arm, as the case may be,

becomes swollen, partly paralyzed and partly held immobile from fear of contacts, the bones atrophied and the skin pale or red and as a rule thin and hypersensitive.

All such changes appear to be due to a sensory-sympathetic reflex which begins in the sensitive nerves of the blood vessels already described, passes inward to make a connection with outgoing sympathetic fibers and finally travels peripherally in the form of an unnatural sympathetic impulse. Whether the impulse must pass through a segment of the cord and thence out through a sympathetic ganglion or may go no farther centralward than a plexus on a large artery is immaterial. It is enough to know that it can almost always be broken by interrupting the sympathetic nerve supply to the affected limb by a paravertebral sympathectomy and that it can often be broken by Leriche's [18] periarterial sympathectomy, as of the brachial artery for edemas of the upper limb.

Those who see much of accident and liability insurance matters will realize that these reflex edemas and the related states of painful and hypersensitive limbs offer a serious problem. Many of them are transitory, a few are persistent and all are more or less under the influence of the patient's mental reactions. Perhaps the most generally useful way to manage them is to accept Leriche's view that the sympathetic system is concerned with all pain [19] (and much edema) and to make use of procaine block in studying the individual case. Livingstone [20] discussed such matters in a most informative way. I prefer a paravertebral sympathetic block with procaine hydrochloride to local injection of the anesthetic on the ground that if, as almost invariably happens, paralysis of the sympathetic nerves restores normal sensibility, color and warmth to an extremity, the patient is convinced that normal conditions have for the moment been restored, the ordinary sensibility to touch, pinprick, etc., being present; thus a favorable reaction to a sympathetic block

18. Leriche, R.: Des règles à suivre dans le traitement des fractures articulaires par infiltration novocainique des ligaments et mobilisation active immediate, Presse méd. **45**:873 (June 12) 1937.

19. To one who finds the sympathetic system concerned with many painful states, it is confusing to read Sir Thomas Lewis' observations on the "nocifensor nerves" and their activities (Lewis, T.: The Nocifensor System of Nerves and Its Reactions, Brit. M. J. **1**:431 [Feb. 27]; 491 [March 6] 1937). These he found to be entirely different from the ordinary sensory nerves, though actually they pass through the posterior nerve roots. They have the property of distributing superficial tenderness in response to local injury and when stimulated centrally, cause capillary vasodilatation. But all this is perhaps not related to reflex edema.

20. Livingstone, W. K.: Post-Traumatic Pain Syndromes: An Interpretation of the Underlying Pathological Physiology, West. J. Surg. **46**:341 (July); 426 (Aug.) 1938.

will often, whether or not the block is repeated, start the patient on the road to improvement. If not, a permanent operative sympathectomy may be used. Cures also result from periarterial sympathectomy, presumably because the ingoing impulses of the reflex are interrupted by the procedure.

Allusion has been made earlier (in the section devoted to the edema of disuse and injury) to the edema of sprains. Following the teaching of Leriche,[18] various attempts have been made to break up with the aid of local injections of procaine hydrochloride, especially in the case of sprained ankles, the vicious edema-producing vasomotor reflex which he describes. Some of these have been encouraging (Moynahan [21]), but there is as yet no substantial agreement on the subject.

EDEMAS DUE TO ALLERGY AND INFECTION

These two causes are placed together, because, as the following discussion will show, it is not always easy to distinguish one from the other and, indeed, the two may be combined. Occasional patients infected with the common fungi of the feet suffer from outbreaks of allergic redness and swelling, attacks which pass off rapidly but which may, in a cumulative way, lead to chronic edema (figs. 2 *D* and 6 *C*). It is often difficult to say in any given case whether the attacks are actually due to hypersensitiveness or to secondary infection entering the skin by way of the lesion caused by the fungus. In the latter event, the infection, almost necessarily streptococcic, takes the form of lymphangitis, perhaps both diffuse and tubular, and in this way damages the superficial tissues and cripples the lymph channels. One would suppose that an accurate account of the attacks might distinguish between these causes, but patients are not always reliable observers, and by the time a leg is enlarged and indurated, even ulcerated, the course of the disease can seldom be traced. It was formerly believed that infection entering by way of sores or abrasions was capable, by repeatedly introducing bacteria into the tissues, of leading in time to chronic edema, but it is my impression that fungous infection is a more potent cause. The matter is especially confusing because so many chronically swollen and indurated legs are prone to ulceration anyway, as a result of scratching and accidental trauma.

The following is a case in point.

Case 1.—I. P., an obese woman 36 years of age, had suffered after childbirth from a phlegmasia alba dolens of her left leg, from which she had recovered with only a little residual edema. However, it was the right leg which afterward became elephantiasic, and there may, of course, have been an unnoticed thrombophlebitis on

21. Moynahan, E. J.: Treatment of Acute Sprains by Procaine Infiltration (Leriche's Method), Brit. M. J. **1**:671 (April 1) 1939.

that side. In any event, sores appeared in the lower half of the right leg, and severe inflammatory attacks attended by high fever occurred at intervals of several months (fig. 6 *A* and *B*). During every attack the whole right leg became red and swollen. After each, desquamation occurred. The ulcers were uncontrollable. Epidermophytosis on the foot was unmistakable. Since no treatment which the patient was capable of carrying out caused the ulcers to heal or the attacks to cease, a lumbar

Fig. 6.—*A*, legs of I. P., a patient with edema due to allergy and infection, so permanent as to deserve the name of elephantiasis. Extensive multiple ulcerations are present. *B*, legs of the same patient during a febrile attack (infectious or allergic). *C*, legs of T. H., a patient with allergic edema related to fungi. *D*, legs of R. N. M., a patient with a cavernous lymphhemangioma. Vicarious menstruation occurred from the small dark spots above the knee. (The individual photographs are taken from Homans, J.: Circulatory Diseases of the Extremities, New York, The Macmillan Company, 1939.)

sympathectomy was performed. The idea behind this operation was to change the environment of the organisms by increasing the vascularity of the superficial parts and so to cause the ulcers to heal. Actually, the effect produced was to leave the skin so hot and dry that a condition hostile to fungi was created. At the time of writing, some two years later, only one small ulcer remains, no more attacks have occurred and the leg is distinctly smaller and less hard than before.

The second case to be described is perhaps one of a pure allergic reaction to a fungus, though this is by no means certain, especially because, as already explained, allergic or infectious outbreaks may occur in sporadic elephantiasis in the presence of infection by fungi.

CASE 2.—E. R., a small woman 30 years of age, had attended a gymnasium some eight years earlier and was aware of having acquired a fungous infection of her feet. Two years later, six years before she came under my observation, the lower part of the right leg rather suddenly swelled, and a month afterward the whole leg below the knee became "sore." She went to bed for three weeks. Since that time she had suffered several such attacks, and three weeks before she was first seen by me she noticed an increase of swelling so severe that the leg felt "as if it would burst." She had noticed also two irritated areas, one over the instep and the other on the shin, near the knee. When examined, the skin of the right foot and leg was a little hot and faintly reddened, but since the patient had kept the foot elevated for several weeks, the ankle and calf were only slightly swollen.

About a year and a half later, after a summer vacation during which the leg gave almost no trouble, she suffered the worst attack she had ever experienced. This time both legs swelled acutely. She noticed some tiny blisters on both feet. After a week of swelling, the legs returned to their previous state. Now, the right leg is clearly the seat of chronic edema and slight but noticeable deformity. There is no external sign of epidermophytosis. The patient's hypersensitiveness to fungus is under investigation.

Treatment.—The problem of dealing with allergic states, especially those due to an elusive fungus, is difficult. The patient's reaction to her own fungus should of course be studied, but when no desquamating skin and no thickenings between the toes are present this cannot be done. One must then fall back on a "shotgun" collection of fungi, test with that and if necessary desensitize the patient to the whole group!

I use another method—lumbar sympathectomy. I am not aware that this procedure has before been used to cure epidermophytosis. However, the hot, dry skin of full peripheral vasodilatation is obviously hostile to the growth of a fungus, and the one experience cited here (case 1) is decidedly encouraging. It hardly seems right to recommend lumbar sympathectomy for routine use, for it certainly carries a risk, which in the presence of infection in the corresponding leg may be prohibitive. Probably it should be used only after prolonged treatment of any (bacterial) infection which may be present, in carefully selected cases.

CAVERNOUS LYMPHANGIOMA

A brief account of this peculiar deformity is offered so that comparison can be made with the various states of elephantiasis described. It is of course a congenital malformation. The superficial tissues in the region affected are puffy, presenting a surface which may be smooth or slightly uneven, but the color of the skin is normal. The enlargement may involve a whole foot or hand or only a finger or two.

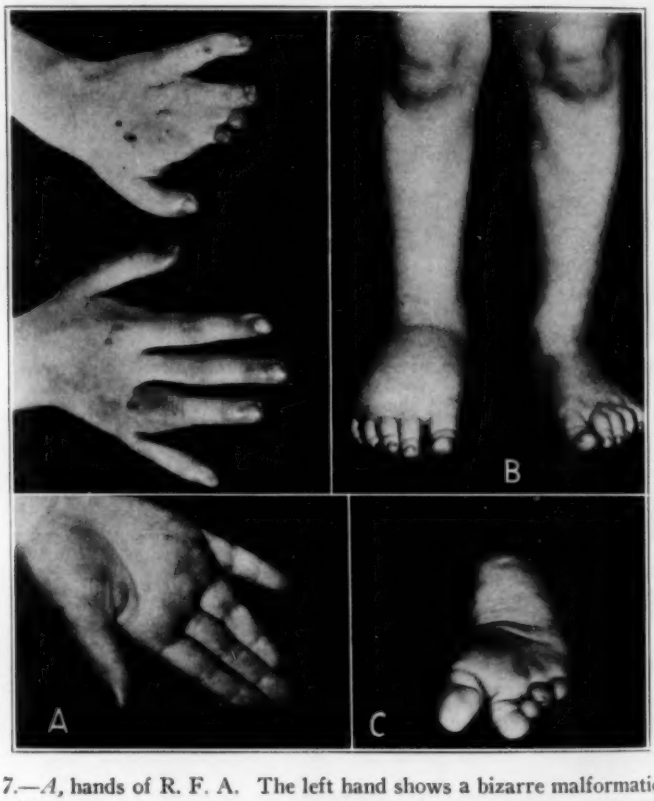

Fig. 7.—*A*, hands of R. F. A. The left hand shows a bizarre malformation. The right hand, which has been photographed from both the dorsal and the palmar aspect, shows a diffuse cavernous lymphangioma and has already been subjected to one operation. *B*, legs of J. B. A., a patient with a cavernous angioma of the right foot. *C*, cavernous angioma at the base of the great toe of G. Huge, deformed toes were associated with the angioma. (The individual photographs are taken from Homans, J.: Circulatory Diseases of the Extremities, New York, The Macmillan Company, 1939.)

The part feels rather boggy and not tense, and the swelling is little affected by elevation or depression. It does not pit like an early edema. Yet if one sees an infant's foot like the one shown in figure 7, one can

hardly be certain, save by the march of events, whether the trouble is one of lymphatic deficiency, the superficial parts being otherwise normal, or whether the tissues superficial to the muscular aponeurosis are malformed. In the first case, the whole leg will present lymphedema and will slowly enlarge; in the second, the change will remain confined to the original area and will only enlarge with growth. Not uncommonly the lymphangiomas of infancy are associated with bizarre malformations of the fingers or toes (fig. 7 *A*, *B* and *C*).

A cavernous lymphangioma often occupies several dermatomes on the surface of a limb; in extreme cases, the whole limb, as is shown in figure 6 *D*. It must be recognized that the superficial tissues are totally changed. They are fluid soaked, fibrosed and very vascular. The aponeurosis beneath may be lacking, so that the abnormal tissue may extend in an irregular, shallow way into the muscle. Thus the removal of the larger lymphangiomas is a difficult matter. It is usually best to remove one bit by bit in a series of minor procedures, especially when it occupies a hand or a foot.

COMMENT

An attempt has been made to sort out and describe the lymphedemas, of the lower limbs especially, which are due to local causes. The elephantiases, that is, those associated with a total disappearance of the lymph vessels, are unexplainable and, as one might suppose, are really incurable: that is to say, there is no way of restoring drainage of the tissue fluids. To do away with the swelling, one must remove the tissue in which fluid collects. This need not, as a rule, be done for the thigh. It is enough to reduce the size of the leg below the knee.

None of the other lymphedemas are wholly of lymphatic origin. Those which originate in femoroiliac thrombophlebitis are certainly due in part to involvement of the larger lymph vessels of the pelvic brim in the perivascular exudate which is so often present in these cases, but venous obstruction (at first) and peripheral vasospasm (later) certainly contribute to the swelling of the limb.

The allergic edemas are undoubtedly going to prove of increasing clinical importance. As yet it is not known whether such states can become established without definite acute attacks of redness, swelling and fever. If edemas of this sort can arise quietly, as it were, then the various fungi of the skin must be even more common and have more access to the internal mechanism than is now believed to be the case. Without proposing to be an alarmist, I deprecate the rather general tendency of members of the medical profession to shut their minds to this matter.

The reflex edemas, that is, the rare and picturesque swellings which arise unpredictably from trivial injuries and infections, seem to be related

to sympathetic control of the peripheral blood vessels. However, their peculiar mode of origin, especially in trauma to certain nerves (the median and sciatic) should make one careful not to be too certain of their nature, and the hypersensitiveness to touch which is so often associated with them appears to give them a relation to the causalgias. There is much to be learned of the relation of pain, superficial tenderness and edema, as a complex, to the somatic and sympathetic nervous systems. The reflex pathways concerned with the reflex edemas and causalgia-like states require especial study.

AMPUTATION FOR PERIPHERAL VASCULAR DISEASE

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In spite of significant additions to the conservative therapy of peripheral vascular disease, such as suction and pressure therapy, intermittent venous hyperemia, iontophoresis with acetylbetamethylcholine hydrochloride (mecholyl) and other measures (the value and limitations of which have been recently analyzed from this clinic [1]), there still remains a group of cases in which amputation must be performed either as a life-saving measure or to rid the patient of a painful and functionless limb which undermines his morale and lowers his earning capacity. It has seemed to us that since the advent of the newer conservative measures, which are urged and demanded by patients even in obviously hopeless cases, patients come later than ever for amputation, thereby increasing the mortality and discrediting the procedure.

In this brief study we wish to present our experience with major and minor amputations done for peripheral vascular disease by ourselves or under our supervision in the five year period from 1933 to 1938. The purpose of this presentation is to emphasize certain procedures which have helped us to establish the indications, to decrease the mortality associated with amputation and to improve the functional status of the patient.

INDICATIONS FOR AMPUTATION

No surgeon has the right to deny the chance for life to a patient, even if the risk is great. The patient's relatives may say that they would rather see him die than lose his leg. There is usually, however, much less opposition from the patient than from the relatives, and if the surgeon convincingly urges amputation the percentage of refusals will not be great.

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1. de Takáts, G.; Beck, W. C., and Roth, E. A.: The Neurocirculatory Clinic: I. Peripheral Vascular Disease, Ann. Int. Med. **13**:957 (Dec.) 1939.

By a "fair chance to save the limb" we mean the following conditions: (1) ability of the patient to have absolute rest in bed and adequate nursing care for approximately three months; (2) absence of any sign of spreading infection (which would indicate immediate amputation); (3) absence of massive gangrene (small gangrenous patches, or true cutaneous infarcts, may slowly fall off and epithelize), and (4) absence of intractable pain or good response to absolute rest, proper postural angle, vasodilators, mild sedatives, passive vascular exercises or paravertebral block with alcohol. When these conditions are not fulfilled, an early amputation lowers mortality, restores the patient's morale and may restore some of his earning capacity.

The last-mentioned benefit should be considered in regard to weight bearing. Most patients above the age of 60 will not learn to use an artificial limb, and a weight-bearing stump need not be considered. Because existence in a wheel chair is dreaded by every one, we wish to present the following case history.

REPORT OF A CASE

Mrs. E. N., 69 years old, diabetic, was suffering from a popliteal atheroma. Although she had no frank gangrene, severe ischemic neuritis was present and was so intractable that an amputation was suggested. It was readily consented to. A Callander amputation was done on March 7, 1938. Twelve days after the operation the patient was walking on crutches. On her discharge from the hospital she was put on a 1,500 calory diet for control of the diabetes, and it was not expected that she would learn to use an artificial limb. However, she appeared in the office three months afterward with an excellent weight-bearing stump, using an artificial limb without a cane or crutches. She was the oldest patient in this series who learned to use an artificial limb.

DETERMINATION OF THE PROPER LEVEL OF AMPUTATION

In a previous communication one of us (de Takáts [2]) pointed out that although the pulses and the color of the limb point to a probably satisfactory level of amputation, the literature contains many reports of reamputations at a higher level which were undertaken because of sloughing of the skin or of the muscles. Our clinic has consistently utilized measurement of cutaneous temperatures and production of histamine flares to determine the level of circulatory efficiency. The patient's lower limbs are exposed to room temperature for fifteen minutes, and the abdomen is heated with a heat cradle to release the vasospastic element. Often a sudden drop in temperature is felt at a certain level, which is then marked with an indelible dye. This level

2. de Takáts, G.: The Determination of the Proper Level of Amputation, Internat. J. Med. & Surg. **47**:339 (Sept.) 1934.

may be a few inches below the hip joint, just above the knee, at the knee or at the midcalf; often in cases of infectious diabetic gangrene the entire leg and foot are warm. Such a finding, as was emphasized by McKittrick and Pratt,[3] permits minor amputation (of toes), which heals well even in the presence of diabetes and in the absence of palpable pedal pulses. Of course, if the pulses of the foot are well palpable and spreading infection is absent, a digital or arteriolar obstruction is obviously present, and minor amputation or spontaneous separation (to be discussed later) is preferable.

The cutaneous temperatures can be determined by a simple mercury thermometer adapted to such use, but when this is not available the palm is capable of detecting sudden drops of temperature. If the fall in cutaneous temperature is gradual, there is really no definite borderline of circulatory efficiency.

Histamine flares are produced by injecting 0.1 cc. of histamine hydrochloride or histamine acid phosphate in a 1:1,000 solution. Ampules containing this amount are readily obtainable on the market. From four to five injections are made, at the usual sites of amputation, such as the midthigh, the lower part of the thigh, the knee, a point 7 inches (17 cm.) below the knee and the dorsum of the foot. A great deal of edema and cyanosis and the pressure of spreading lymphangitis obviously prohibit the use of these injections at the site of the complications. The reaction of the skin to histamine is read in five minutes by determining the size of the hyperemic zone and the intensity of hyperemia or by measuring the rise in cutaneous temperature as suggested by Perlow.[4] The latter procedure is helpful with Negro patients, in whom the arteriolar response to histamine is not visible. A detailed study of the cutaneous reactions to histamine has been published before.[5]

The two tests, namely, determination of the cutaneous temperatures and production of histamine flares, point to the same level almost invariably. When there is not much time to lose, the histamine flares alone have been utilized.

On the basis of several hundred such determinations we have concluded that a positive reaction to histamine insures a viable skin flap, provided no severe infection or undue tension of skin sutures occurs. A negative reaction to histamine does not exclude the possibility that

3. McKittrick, L. S., and Pratt, T. C.: Principles of and Results After Amputation for Diabetic Gangrene, Ann. Surg. **100**:638 (Oct.) 1934.

4. Perlow, S.: The Temperature of the Flare as an Index of the Intensity of the Histamine Skin Reaction, Am. Heart J. **11**:605 (May) 1936.

5. de Takáts, G.: The Cutaneous Histamine Reaction as a Test of Collateral Circulation, Arch. Int. Med. **48**:769 (Nov.) 1931.

a well healing stump may occur. In fact, some years ago Smith [6] of New York, demonstrated to one of us his excellent technic of amputation of the lower part of the leg at a level at which the reaction to histamine was negative. His delicate technic and careful attention to minute detail insure wound healing under doubtful circumstances. In our experience, however, this amputation did not result in primary union in the type of patients referred to us for amputation. After amputation at a level at which histamine flares were obtained we have not seen any sloughing. The reason for marginal necrosis will be discussed in the technical part of this paper.

PREPARATION OF THE PATIENT

Patients who are to have an amputation fall roughly into two classes. First, there are the septic, dehydrated patients, who must be prepared with a sufficient amount of fluids, often with transfusions; if diabetes is present the acidosis at least should be controlled.[7] Because gangrenous parts so often harbor anaerobic bacteria, our standing order is to give two prophylactic doses of polyvalent anaerobic serum. It must be emphasized that a positive culture of Clostridium welchii does not mean a clinical infection with this organism; nevertheless, the high mortality of gas gangrene following amputation [8] (59 per cent for the entire group and 75 per cent for diabetic patients) makes it imperative that the incidence of postoperative gas gangrene should be minimized. There is good evidence now of the value of serum in cases of gas gangrene, both in prophylactic and in therapeutic doses.[9] In 2 patients of this series fulminating gas gangrene developed. The older, a 65 year old diabetic patient, died; the younger, 45 years old, suffering from thromboangiitis obliterans, recovered after use of massive amounts of serum, administration of sulfanilamide and wide exposure of the intramuscular spaces. This experience makes us wonder whether the prophylactic dose ought not to be raised to a

6. Smith, B. C.: Amputation Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene, Arch. Surg. **27**:267 (Aug.) 1933.

7. de Takáts, G.: Surgery in Diabetes, J. Kansas M. Soc. **36**:177 (May) 1935.

8. Eliason, E. L.; Erb, W. H., and Gilbert, P. D.: The Clostridium Welchii and Associated Organisms: Review and Report of Forty-Three New Cases, Surg., Gynec. & Obst. **64**:1005 (June) 1937.

9. Bates, M. T.: Gas Gangrene: A Review of Thirty-Two Cases with Special Reference to the Use of Serum, Both Prophylactic and Therapeutic, Ann. Surg. **105**:257 (Feb.) 1937. Mitchell, O. W. M.; Bryant, T. L., and Chapman, O. D.: Gas Gangrene: Morbidity and Mortality in New York State, New York State J. Med. **38**:1015 (July 15) 1938.

therapeutic one before the operation;[10] the trauma of the operation and especially a tight closure of the stump in poorly vascularized areas can readily activate the "resting" infection in the tissue spaces.

Because of the remarkable results obtain by Kelly [11] in the treatment of gas gangrene with roentgen rays, we have also used prophylactic irradiation of the site of amputation in a few cases. The value of the procedure cannot be estimated from our limited material, as the incidence of gas gangrene following amputations in our series was not high; in a series observed at the Philadelphia General Hospital [8] gas gangrene followed 67 per cent of amputations. When portable apparatus becomes generally available for prophylactic irradiation, more general use can be made of this method.

The second group of patients requiring amputation are not in immediate danger as to life. Their limbs are useless and intractably painful; their morale is shattered, and not infrequently they come to us loaded with opiates. If there is a little time to spare, one can try to break the drug addiction, at least in part, before the amputation, because the psychic shock of amputation together with sudden withdrawal of morphine or pantopon (a mixture of hydrochlorides of opium alkaloids) a few days after the operation produce a difficult situation. Sodium bromide both before and after the operation has seemed helpful. We would warn against the use of scopolamine for elderly patients as a preoperative medication; it seems that patients with cerebral arteriosclerosis or any other disturbance of cerebral circulation show a profound response to scopolamine. They may be difficult to arouse for twelve to twenty-four hours after injection of $\frac{1}{200}$ grain (0.3 mg.) of scopolamine, which is obviously undesirable. For patients under spinal anesthesia, $1\frac{1}{2}$ grains (96 mg.) of pentobarbital sodium is sufficient; for patients under general anesthesia, a small dose of morphine with $\frac{1}{150}$ grain (0.4 mg.) of atropine.

The preparation of the field needs some comment. Errors are frequently made in too extensive or too neglectful cleansing of the skin. The part to be removed should be carefully wrapped in cotton and gauze bandage and the edges bordering the surgical field glued to the skin with a 40 per cent solution of mastic in benzene. A soap and water preparation the night before and a gentle swabbing with alcohol in the operating room are sufficient. Iodine, especially in devascularized areas, does more harm than good. In amputations at the level of the midcalf or of the thigh the use of iodine is less objectionable

10. This suggestion has been recently made by Callander and his associates (Am. J. Surg. **42**:811, 1938).

11. Kelly, J. F.: The Present Status of the X-Ray as an Aid in the Treatment of Gas Gangrene, Radiology **26**:41 (Jan.) 1936.

but does not seem essential. A 2 per cent solution of brilliant green (a basic dye, the sulfate of tetraethyldiaminotriphenylmethane) may be conveniently used to outline the flaps.

ANESTHESIA

In our experience, spinal anesthesia is the method of choice for major amputations of the lower extremities; even midtarsal or toe amputations may be done well with small doses of a spinal anesthetic. For the spinal anesthetic from 100 to 120 mg. of crystalline procaine hydrochloride dissolved in 2 to 3 cc. of the patient's spinal fluid is used; the blood pressure is maintained with 0.5 cc. of a 1 per cent solution of neo-synephrine hydrochloride; this is given just before the lumbar puncture, and the dose may be repeated when the blood pressure falls below the preoperative level.[12] The anesthesia so induced disturbs the patient's chemical equilibrium the least; diabetic patients may be fed by mouth a few hours after the operation. It has been our cus-

TABLE 1.—*Methods of Anesthesia in Amputations for Peripheral Vascular Disease*

Type of Amputation	Anesthesia			Total Number of Cases
	Spinal	General	Intravenous	
Major	38	10	2	50
Minor	2	3	7	12

tom to insist on this type of anesthesia except in the following instances: (1) when the patient absolutely refuses spinal anesthesia, (2) when the patient is septic or comatose, in which case a very rapid amputation is done with the use of a small amount of ethylene, and (3) when the operation is so short that a small intravenous dose of pentothal sodium (sodium ethyl [1-methylbutyl] thiobarbiturate) suffices. Table 1 gives these data in detail.

METHODS OF AMPUTATION

With the exception of a few amputations of the upper extremities, which we are not reporting here, four types of amputation have been done in cases of peripheral vascular disease, namely, metatarsal amputation, amputation of the lower part of the leg, transcondylar amputation and supracondylar amputation. "High thigh" amputation was necessary in a few cases of embolic obstruction of the common iliac artery.

Metatarsal Amputation.—Great credit is due to McKittrick,[13] who in repeated publications has emphasized the important distinction between

12. Brunner, R., and de Takáts, G.: The Use of Neosynephrine in Spinal Anesthesia, Surg., Gynec. & Obst. **68**:1021 (June) 1939.

13. McKittrick, L. S.: Indications for Amputation in Progressive Arterial Obliteration of the Lower Extremities, Ann. Surg. **102**:342 (Sept.) 1935.

infectious and circulatory gangrene. This is especially significant in cases of diabetes. A toe may be gangrenous because of an infected callus propagating infection toward the bone, with production of osteomyelitis, which in turn produces edema, thrombosis of digital vessels and the appearance of a sloughing defect. In such cases the pedal pulses may be impalpable, but the metatarsal region is warm; in fact, there is evidence of inflammation (rubor and pus formation). The reaction to histamine on the dorsum of the foot is positive. The patients, having been immobilized in bed for several weeks, resting on their heels, have deep abscesses under the plantar fascia, which may

Fig. 1.—*A*, roentgenogram of the right foot of Eliza C., a 65 year old Negress. Note the subluxation of the third toe, which was not disturbed and did not interfere with walking. *B*, right foot of the same patient. The scar lies anterolaterally and is not painful. The patient walks on this foot without any discomfort or orthopedic appliance.

be easily overlooked and which may finally lead to loss of the foot. Even elderly diabetic patients tolerate the removal of one or more toes and make a good functional recovery if these abscesses under the plantar fascia are looked for and adequately drained. In the case of E. C., a 65 year old Negress, a metatarsal amputation of the first and second toes was performed. In order to get satisfactory anteroposterior drainage, the first metatarsal bone had to be amputated at a fairly high level (fig. 1 *A*). After a long convalescence, the foot healed

well, and the patient has been repeatedly examined, the last time being two years after the operation. She wears a metatarsal pad in her shoe (fig. 1 *B*).

In cases of Buerger's disease it is usually wise to wait for demarcation of a gangrenous phalanx; when the whole digit is involved, causing intractable pain and threatening ascending infection, metatarsal amputation shortens functional and economic inefficiency. The flaps in such cases must be loosely sutured with a few interrupted sutures, without tension or drainage. In 2 recent cases a lumbar sympathectomy was performed prior to such an amputation; it markedly improved the collateral circulation at the level of amputation, increasing the chances of healing (fig. 2).

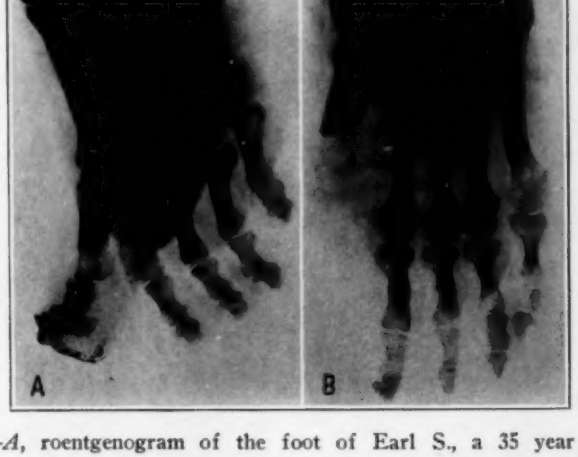

Fig. 2.—*A*, roentgenogram of the foot of Earl S., a 35 year old patient suffering from Buerger's disease. *B*, same foot after amputation. The wound healed slowly four weeks after amputation. Lumbar sympathectomy preceded the amputation.

For embolic gangrene of the toes a metatarsal amputation may be attempted, provided that a fair collateral circulation has developed down to that level. If the gangrene is dry and shows no signs of infection, from fifty to one hundred hours of intermittent venous hyperemia[14] may help to develop the collateral circulation. Unfortunately, the feet in such a case are useless because of ischemic nerve paralyses or tendon contractures, so that a minor amputation can seldom be carried out.

14. de Takáts, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, J. A. M. A. **108**: 1951 (June 5) 1937.

The worst chances for a successful minor amputation are found in cases of arteriosclerosis. This is in accordance with McKittrick's statistics.[13] It means that once amputation has been decided on, the metatarsal level is usually too low; even if the wound slowly heals, the stump is painful and cold and the foot useless for locomotion. Barring an exceptional case, this amputation is not apt to succeed and will have to be followed by a high amputation.

"Lower Leg" Amputation.—Amputation of the lower part of the leg has obvious advantages over amputation through or above the knee. The associated mortality is lower, and preservation of the knee allows far better locomotion than is possible if the knee has to be sacrificed. It is far more difficult, however, to construct a satisfactory stump for patients suffering from peripheral vascular disease. An adequate muscular and fascial covering for the tibia, even when its crest is well chiseled off, is desirable; on the other hand, suture of the fascial planes in amputation for peripheral vascular disease increases the percentage of infection and mortality, as has been brought out by Taylor.[15] The ingenious method of Smith[6] does away with a number of objections to amputations below the knee. He[16] has recently reported on twenty such amputations for diabetic gangrene, with a mortality of 18.1 per cent. In a recent personal communication he reported 41 such amputations, with a mortality of 11 per cent; 95 per cent of the patients could wear an artificial limb. These results are so striking that an attempt should be made to reproduce them elsewhere. Our experience with this type of amputation is so small that it cannot be used for statistical purposes. Of the 3 patients in whose cases it was tried, 2 (with diabetes) died, probably owing to the increased trauma and the more difficult conditions of drainage following the operation. Recently, however, 5 such amputations were performed without mortality and with excellent functional results. For the material that we are dealing with, amputation of the lower part of the leg cannot often be considered. The patients either come to us with an ascending infection originating from preexisting gangrene or with such poor collateral circulation that an amputation below the knee cannot be successfully performed. For this reason we have become more and more convinced of the value of the transcondylar amputation of Callander.

Callander's Amputation.—Most authors dealing with arteriosclerotic patients with or without diabetes agree that when amputation of toes

15. Taylor, F. W.: Amputation Stump of Arteriosclerotic Gangrene, Surg., Gynec. & Obst. **67**:114 (July) 1938.

16. Smith, B. C.: The Therapy of Surgical Complications of Diabetes Mellitus at Presbyterian Hospital in New York City, 1930-1935, Surgery **2**:509 (Oct.) 1937.

is impossible the level of circulatory efficiency is at the knee. Among the many cases in which we have used histamine flares since 1930 there were only a few instances in which the flares were normal below the knee. Before the introduction of Callander's method [17] amputation in such cases was done at the lower third of the thigh by the circular, or flap, method. Of 21 patients so treated, 7 died, a mortality of 33.3 per cent. In a comparable group of 26 patients amputation was done by Callander's method, with death of only 2 patients (7.6 per cent). These figures, however, hardly express the superiority of the method because of the weight-bearing ability of the stump, the lack of infection of the stump and the absence of need for secondary amputations.

Although the method has been twice described by Callander, its general use, as far as we can tell, is still delayed. Because it has given such satisfactory results in our hands, we wish to draw attention to it again. The method has not been modified, although a few insignificant points have been added to it.

Figure 3 shows the outline of the flaps, which we prefer to mark with a 2 per cent aqueous solution of brilliant green. These lines are shown as originally described by Callander, the posterior flap extending more distally than the anterior. In the 3 instances of marginal necrosis that were encountered the condition occurred on the posterior flap. This flap extends so far down and its viability can be so easily injured that it seems wise to make the two flaps extend distally to the same level, namely, to the tuberosity of the tibia.

In figure 4 *A* the four internal hamstring muscles have been cut and are seen to retract. This, together with the severing of the adductor magnus muscle close to its femoral insertion, opens up the popliteal space, which can be approached at this point in the operation or, preferably, when the lateral wall of this space has been entered.

In figure 4 *B* the popliteal space has been entered from the lateral side after the cutting of the tendon of the biceps femoris muscle and the iliotibial tract. The nerve is cut and seared with electric cautery, and alcohol is not injected into it. This, we believe, diminishes the incidence of fantom limb pain and the incidence of neuromas. The use of the cautery was described by Hedri [18] many years ago, and we have used it for several years. The artery and vein are tied separately with silk and transfixed with a silk suture; if they are closely matted together, as they often are, they may be tied and transfixed en masse.

17. Callander, C. L.: A New Amputation in the Lower Third of the Thigh, J. A. M. A. **105**:1746 (Nov. 30) 1935; "Tendoplastic" Amputation Through the Femur at the Knee: Further Studies, ibid. **110**:113 (Jan. 8) 1938.

18. Hedri, A.: Ein einfaches Verfahren zur Verhütung der Trennungsneurome, Verhandl. d. deutsch. Gesellsch. f. Chir. **45**:50. 1921.

Next, the knee joint is entered through the anterior flap (fig. 4 *C*). The patella is excised by sharp dissection, care being exerted not to injure the patellar ligament, which is later used to cover the sawed end of the femur. No attempt is made to remove the synovial membrane, as it does not seem to interfere with prompt healing. The posterior flap is then prepared, and the femur is freed just above the condyles, at a level shown in figure 3, which is lower than in the usual supracondylar amputations. This results in a wider and heavier weight-bearing surface. The bone is sawed off after a subperiosteal cuff is formed. The bone marrow is not disturbed.

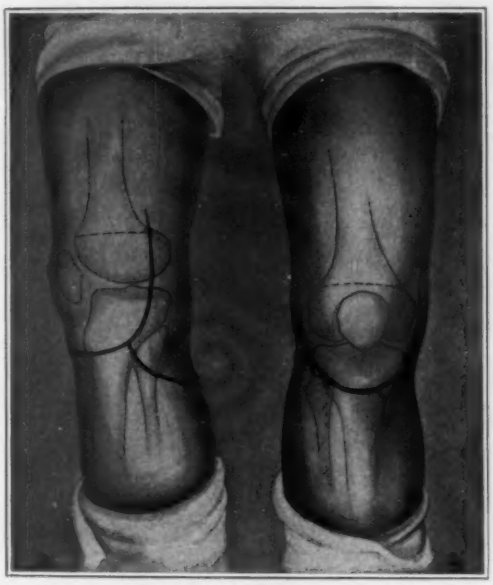

Fig. 3.—Outline of skin flaps for the amputation described by Callander. *A*, lateral view; *B*, anteroposterior view. The anterior flap is started about 4 fingerbreadths proximal to the internal condyle of the femur, at the well palpable border of the quadriceps femoris muscle. It swings around through the level of the tibial tuberosity to the lateral border of the quadriceps muscle, ending at the same height as on the medial side. Note that the posterior flap originates at right angles from the anterior flaps and reaches farther distally. This may be the reason, together with a possible operative injury to the collateral arteries of the knee, for the occasional marginal sloughing of the posterior flap.

Figure 4 *D* illustrates the loose approximation of the two flaps by a few skin clips. No suture has been placed into tendons or ligaments. Copious drainage occurs for a few days after this amputation. A drain may be placed under the posterior flap for a day or two. It must not endanger the viability of the posterior flap. Although the flaps look far

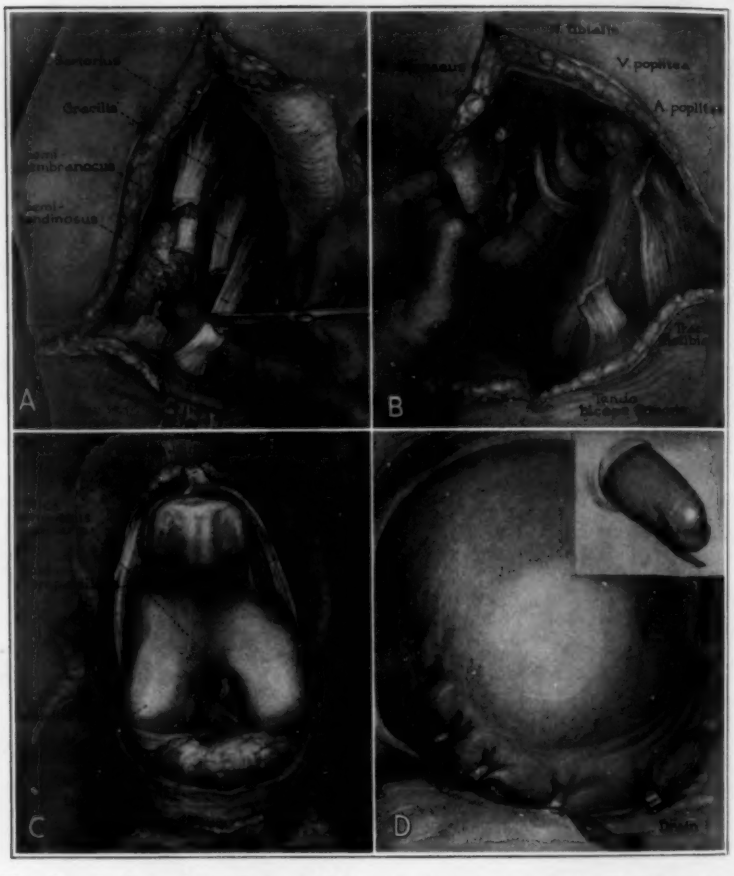

Fig. 4.—*A*, deepening of the incision of the anterior flap. The four internal hamstring muscles have been picked up and cut close to their insertion. They readily retract from the wound. Not shown here is the insertion of the adductor magnus muscle on the femur, which is also severed. *B*, exposure of the popliteal fossa from the lateral side. The tendon of the biceps femoris muscle and the iliotibial tract have been cut. The sciatic nerve or its two divisions are severed with the electric cautery. The vessels are tied with silk and transfixed to prevent slipping. *C*, exposure of the knee joint through the anterior flap. The patellar ligament is carefully saved, but the patella is discarded. The femur is sawed off just above the cartilage, and the patellar fossa is fitted into the sawed surface. *D*, final stage of the operation. The two flaps are allowed to fall together. No sutures are placed in the patellar ligament. Only a few skin clips are placed to approximate the edges of the skin. If there is a large dead space under the posterior flap, this may be drained for twenty-four hours. Copious drainage occurs between the skin clips; when this subsides, in four to five days, more clips are applied for accurate closure of the wound. The flaps, which at first seem far too long, rapidly retract.

too loose for a few days, an astonishing amount of retraction takes place in the posterior flap, so that the suture line is far enough from the weight-bearing surface (fig. 5).

MORTALITY STATISTICS

Excluding amputations of toes and metatarsal amputations, which were followed by no deaths, we are presenting our data on 50 major amputations. Of the 50 patients, 14 died, a total mortality of 28 per cent (tables 2 and 3). This is lower than the figures from the Philadelphia General Hospital [8] and those from the Cook County Hospital

Fig. 5.—Amputation stump ten days after a Callander amputation. Ten days later a temporary peg leg was applied. The mobility of the flaps and the painless, direct weight-bearing stump always astonishes the makers of the artificial limb.

in Chicago [19] but much higher than the figures of McKittrick [13] and those of Smith.[16] Although the number is too small to warrant statistical analysis of such factors as age, infection, absence or presence of diabetes and absence or presence of arteriosclerosis, it is obvious that advanced age, diabetes and extensive cardiac damage, but especially generalizing sepsis, raise the mortality rate. We were interested, however, in dividing these cases according to the type of amputation performed (table 4). At present we have not enough experience with the

19. Apfelbach, G. L.: The Surgical Management of Lesions Peculiar to Diabetes Mellitus, Illinois M. J. **56**:332 (Nov.) 1929.

technically delicate amputation of Smith to express any opinion on it, but the difference in results between the customary "low thigh" amputation and the Callander amputation is striking. The mortality rate dropped from 33 per cent to 7.6 per cent, although the selection of cases, the material and the surgical personnel were the same during the five year period. The Callander amputation provides for copious drainage for the first few days without sacrificing stump length and also without prolonging the stay in the hospital, as secondary closure is easily accomplished. A comparison of the period of hospitalization with the two amputations shows that after twenty-one amputations at the lower part of the thigh the average number of days in the hospital was twenty, as compared with a stay of eleven days after twenty-six Callander amputations. Some patients were discharged as early as six days after the operation.

TABLE 2.—*Causes of Death Following Amputation for Peripheral Vascular Disease*

	Number of Deaths
Bronchopneumonia	2
Coronary occlusion	2
Delayed shock	1
Cardiac failure	1
Sepsis	8
Total	14

TABLE 3.—*Types of Gangrene Necessitating Major Amputation**

Gangrene	Number of Cases	Number of Deaths
Diabetic	30	10
Arteriosclerotic	11	2
Postembolic	6	2
Post-thrombotic	3	0
Total	50	14

* In no case of Buerger's disease was amputation performed above the metatarsal level.

TABLE 4.—*Mortality Following Various Types of Amputation*

Type of Amputation	Number of Cases	Percentage of Deaths
Metatarsal	15	0
Lower third of thigh	21	33
Callander	26	7.6
Total	62	14.5

EMERGENCY AMPUTATIONS

When patients are first seen in a septic, dehydrated, sometimes comatose or delirious, state, little time should be lost in performing an emergency amputation. We have been repeatedly amazed at the effect

of such an amputation on a comatose, moribund patient. Obviously the mortality rate of such amputations is higher; the mortality rate of our deliberate amputations was 14.5 per cent, while that of 15 emergency amputations was 33 per cent. We feel, however, that in the last year we have decreased this mortality by (1) doing a rapid guillotine amputation below or above the knee in eight to ten minutes; (2) using morphine-scopolamine premedication and a slight quantity of nitrous oxide with plenty of oxygen for the anesthetic; (3) giving transfusions, sulfanilamide and anti–gas gangrene serum before and after the operation, and (4) leaving the stump wide open, without a single suture, and using dependent drainage instead of the frequently employed elevation of the stump.

It is difficult to foresee when a gangrenous leg will become suddenly a source of general septicemia and toxemia. The patient may be admitted to the hospital in good general condition, with a slight fever in the evening or none at all and with moderate leukocytosis. Within a day or two the patient may suddenly become septic, and one has a feeling that valuable time has been lost. Although preparation with anti–gas gangrene serum and diabetic control are, of course, desirable, no time should be lost if septicemia is threatening or is present. The best treatment for the patient's diabetes is to get rid of the source of infection, and only the acidosis needs to be controlled.

REAMPUTATIONS

Stumps may have to be reamputated because of tight skin, spurs, neuromas or marginal necroses of bone, but in cases of vascular disease a problem arises regarding the secondary closure of guillotine amputations. Guillotine amputations through the lower part of the leg or the thigh have occasionally been done on septic, comatose patients under gas anesthesia of short duration; it is remarkable how these severely handicapped patients tolerate such a rapid amputation. It is customary, however, from two to three weeks after this operation to resect the protruding bone and close the skin over it. Such operations frequently result in a flare-up of the latent infection, which necessitates reopening of the stump and results in further delay in healing. Of 8 cases of guillotine amputations in which the stump was subjected to secondary closure, a marked flare-up occurred in 4; 1 patient, seen in consultation in another service, had general septicemia. We have come to the conclusion that skin flaps should be prepared at the first operation. Should the shrinkage be so extensive that secondary closure is impossible, it is better to use skin grafts to cover the stump than to reamputate through a previously infected field. Another method used was to do a Callander amputation after a guillotine amputation through the lower part of the leg. By this method the infected field is not reentered.

THE ARTIFICIAL LIMB

If primary union takes place, a temporary peg leg is constructed and worn by the patient within four to six weeks. Patients above the age of 65 years, with some notable exceptions, hardly ever learn the use of an artificial leg. In table 5 we give the number of patients who have received and used a prosthesis after amputation. Again the superiority of the Callander type of amputation is evident, although, as Smith [16] has repeatedly pointed out, patients whose legs have been amputated below the knee by his modified guillotine technic have worn prostheses in about 95 per cent of cases; about 90 per cent of his patients whose legs have been amputated at the thigh could not or would not wear a prosthesis, but the amputations were not done with the Callander technic.

The cause of refusal to wear an artificial limb, excluding senility, other incapacitating illnesses and financial difficulty, lies mostly in the

TABLE 5.—*Use of Artificial Limb*

Type of Amputation	Number of Patients Traced	Wearing Limb
Lower part of leg	3	2
Lower third of thigh	14	8
Callander	20	16
Total	37	26

stump itself or in the indifference of the surgeon toward urging functional rehabilitation. Finally, there is the condition of the other limb.

FATE OF THE OTHER LIMB

Except when there is embolic occlusion in one limb, it is a general rule that the limb remaining after amputation suffers from impairment of circulation, although frequently in a much less advanced form. With the help of pulses, oscillometric curves, histamine flares and sudden changes in cutaneous temperature, one should be oriented as to the stage of vascular impairment. That the heel and all bony prominences should be protected while the patient is bedridden is obvious. We have made routine use of intermittent venous hyperemia [14] before and after amputation of the other limb. Nevertheless, because of the strain on the single leg, we have seen a number of patients return with a rapid exacerbation of the vascular status of the remaining leg. For this reason the status of the remaining leg must be thoroughly considered before the use of an artificial limb is urged. Actually, of the 50 cases in this series the other limb was later amputated in only 3, but this does not indicate the percentage of limbs which subsequently become gangrenous.

COMMENT

Such a mutilating operation as amputation is unwelcome to both patients and surgeons. It is unavoidable, however, in case of sudden raterial occlusion that could not be or was not subjected to embolectomy or of chronic vascular occlusion for which effective conservative treatment was not started in the early stages. A diagnosis of "rheumatic pains" or "flatfoot" is still made too often in the early stages of peripheral vascular disease, and much valuable time is lost by ineffective or harmful measures. A combination of sympathectomy and amputation of toes might also save from major amputations a number of patients suffering from advanced forms of Buerger's disease.

Fig. 6.—Massive gangrene of the right leg. Miss M. H., 80 years old, mildly diabetic, had a small gangrenous patch over a bunion. The gangrene rapidly spread, producing profound toxemia. With adequate diabetic control and fluid intake she was kept alive for several weeks. She died of acute coronary occlusion. Amputation was not attempted. (Case of Dr. George H. Coleman.)

Few patients are so independent financially that rest in bed for months in a favorable climate with adequate nursing care is feasible. The urgency of restoring the patient's earning capacity should always be kept in mind. Massive gangrene calls for prompt amputation except in cases of extreme senility (fig. 6), as a well localized dry gangrene may develop overnight into rapidly progressive toxemia and septicemia, with an increased rate of mortality and need for prolonged hospitalization. Although the utmost conservatism must be observed in advocating the loss of any part of the extremities, no time should be lost in removing a part which is obviously lost and which no magic can recover.

For several years we have kept records (1) of patients who were urged to have an amputation but refused when first seen and (2) of the financial strain which the patient has shouldered before he submitted to amputation. Of the 10 patients who were urged to have a major amputation and refused, 3 returned within six months to us, 4 had an amputation elsewhere and 3 could not be traced. Among 15 patients on whom data in regard to medical expenses are available, three groups were established. Five patients who were unemployed or earned less than $100 a month were on relief from two to four years because of inability to work; 3 of these were rehabilitated and regained their earning power. Seven patients whose income was from $150 to $300 a month had spent from $1,500 to $3,500 (approximately one year's income) for medical care and were devoid of reserves when they came to amputation. Three patients in the upper brackets of income had spent an average of $5,000 to save an obviously lost extremity.

We wish to make it clear that we do not refer to patients who with conservative therapy (in which we include sympathectomies and amputation of digits) have a fair chance to retain the limb. The crux of the situation lies in defining this "fair chance to save the limb," as in the other two groups, namely, patients with good collateral circulation and patients with massive gangrene and increasing toxicity, the indications are well defined and need no elucidation.

SUMMARY

The indications for amputation and the methods and results of amputations done in certain cases of peripheral vascular disease have been discussed. Determination of the proper level of amputation and preparation of the patient are described. Factors decreasing mortality are emphasized. The study was based on 50 major amputations. Although a mutilating operation, amputation for vascular disease continues to rehabilitate economically handicapped or seriously endangered patients for whom conservative measures are ineffective. The mortality can be reduced to a small, unavoidable percentage, especially by amputating before infection is superimposed on gangrene.

PERIARTERITIS NODOSA SIMULATING AN ACUTE ABDOMINAL CONDITION REQUIRING OPERATION

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Periarteritis nodosa was first accurately described by Kussmaul and Maier [1] in 1866. Since that time, many detailed case reports have appeared in journals devoted to pathology or to internal medicine. The frequency with which this disease simulates acute conditions requiring surgical treatment justifies its emphasis in the surgical literature.

Periarteritis nodosa or, better, polyarteritis nodosa, is primarily a disease process involving the walls of blood vessels. The lesions start with edema and subsequent necrosis in the media of the vessel wall. The process ultimately extends to the intima, with reactive cellular proliferation which frequently produces endothelial injury and thrombus formation. There is also an adventitial infiltration of polymorphonuclear leukocytes, often accompanied by eosinophils. The healing process with the laying down of connective tissue results in the formation of a nodule involving the vessel wall; lack of repair, mural degeneration and necrosis with destruction of elastic fibers may terminate in aneurysm formation. Nodule formation may also be due to a prominent cellular infiltrate without fibrous tissue proliferation, as was seen in a number of the involved vessels in the case reported here. There is often observed in the vicinity of the cellular infiltrate and necrosis a fibroblastic proliferative intimal response. These lesions have a distinct predilection for the arterial side of the circulation, although involvement of venous walls has occasionally been observed. The medium-sized and smaller arteries are predominantly the site of the lesions. In the cases reported in the literature, the vessels of the lungs, central nervous system and bones seem to be infrequently affected, while the renal arteries are almost invariably involved.

REPORT OF A CASE

W. W., a small white man, was admitted to the medical service of the Knickerbocker Hospital on April 29, 1939. The past history was irrelevant except for gonorrheal urethritis in 1932. This had been treated and cured. The present

1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1866.

illness started six weeks prior to the patient's admission to the hospital, when there was a sudden onset of severe pain in the back. This was followed in a few days by cloudiness of the urine. Within two days the pain radiated into both flanks and the upper part of the abdomen, and a few days later it progressed to the lower part of the abdomen and into the testicles. The patient was constipated at that time and took castor oil, after which there was a very dark stool. He visited the outpatient department of another hospital and was told he had an ulcer of the stomach, although no roentgen or laboratory studies were made. Medicine was prescribed, and immediately after taking it he began to vomit. Three weeks before admission he stated that the pain had left the lower part of the abdomen and localized in the right upper quadrant. He then began to have daily chills, after which he felt feverish. He continued to vomit frequently and lost 30 pounds (13.6 Kg.) in the six weeks prior to admission. An increase in severity of the pain in the right upper quadrant caused him to seek care in the hospital.

The patient appeared chronically and acutely ill. The positive findings were limited to the abdomen and back. There was tenderness throughout the abdomen, most marked in the right upper quadrant, and in this area there were muscle spasm and rebound tenderness. There was tenderness in both costovertebral angles, more marked on the right side. Tenderness on pressure was elicited over the lower border of the liver, which was about 1 inch (2.5 cm.) below the costal margin. The knee jerks were exaggerated, and the lower abdominal reflexes could not be obtained. The temperature was 101 F. on admission and ranged irregularly between 100 and 102 F. The blood pressure in millimeters of mercury was 102 systolic and 78 diastolic. The pulse rate was 90 per minute. The erythrocyte count was 3,850,000 per cubic millimeter of blood, with 76 per cent hemoglobin. The leukocyte count was 18,000 per cubic millimeter, with 96 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood was negative. The value for nonprotein nitrogen was 27 mg. per hundred cubic centimeters. Repeated urinalyses revealed no abnormality. The benzidine reaction for blood in the stool was 4 plus. Five days later this reaction was negative.

The patient was seen by members of the medical and surgical staff, and the diagnoses considered included right perinephric abscess, appendical abscess and cholecystitis. Forty-eight hours after admission, the rigidity of the right upper quadrant became boardlike, and one of the surgeons felt that he was dealing with a penetrating peptic ulcer. During the next week the rigidity of the right upper quadrant persisted, and nine days after admission the abdomen was explored. At operation numerous adhesions were found between the omentum and the anterior abdominal wall. There were a normal-appearing appendix and a markedly thickened gallbladder about one and a half times the normal size, surrounded by a few adhesions. The stomach appeared normal. A cholecystectomy and an appendectomy were performed, and material for biopsy was removed from the liver. The true diagnosis was made on microscopic examination of the specimens, the lesions being found in the arteries of the gallbladder, appendix and liver (figs. 1 and 2). The arterial walls showed cellular infiltration of fibroblasts, reticulum cells and a few polymorphonuclear leukocytes. No eosinophils were seen. This infiltration involved the entire wall of the artery and extended into the perivascular tissue. Some vessels showed areas of fibrous replacement of their various layers. No aneurysms were encountered. The vascular lesions of the liver were within the portal fields and were confined chiefly to the arteries. In this viscus the periadventitial infiltration frequently exceeded that within the

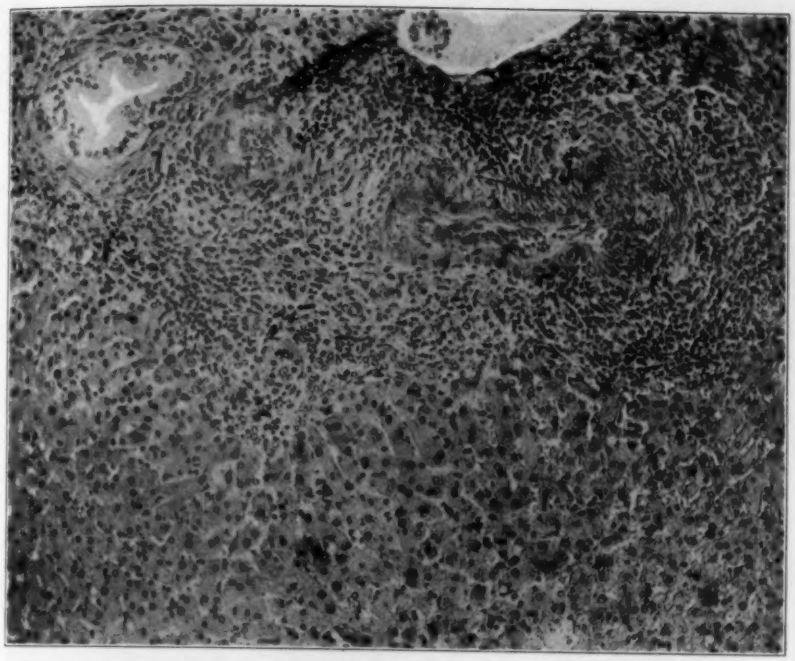

Fig. 1.—Low power photomicrograph of the liver. The arterial wall shows the subacute (organizing) type of lesion.

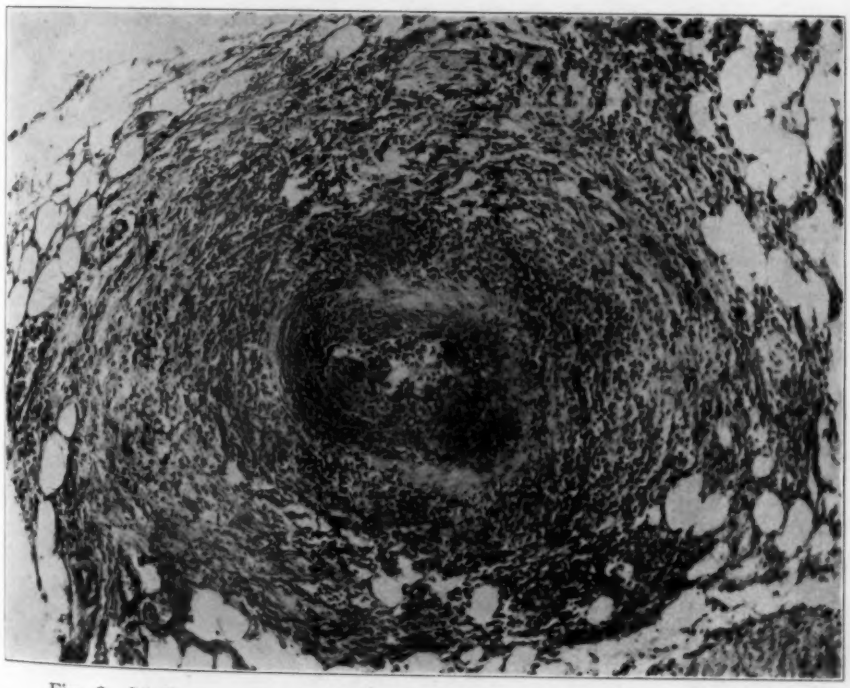

Fig. 2.—Medium power photomicrograph of a medium-sized artery in the appendical serosa, showing the typical lesion of periarteritis nodosa. Note the extensive necrosis, diffuse cellular infiltration and thrombus formation.

vessel wall. In one area of the liver an adjacent venule in the portal field was found to be involved. Evidence of subacute perihepatitis was noted. The wall of the gallbladder showed evidence of reactive acute and chronic inflammation, evidently the sequel of the vascular lesions. Postoperatively, the patient made a remarkably uneventful convalescence. In spite of transfusions the erythrocyte count and the hemoglobin concentration remained low, and the leukocyte count averaged about 12,000 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. Numerous differential studies of the blood smears revealed from 2 to 6 per cent eosinophils. Repeated chemical studies of the blood showed

Fig. 3.—Heart. Note the increased prominence and nodular thickening of the branches of the coronary arteries, the pericardial scars and the multiple pericardial hemorrhages. The central zone of pericardial thickening indicates the site of a myocardial infarct.

values within the normal range for nonprotein nitrogen, uric acid and creatinine. The patient was discharged to a convalescent home on May 28.

He was readmitted to the hospital on August 2. At this time he presented a picture of chlorotic marasmus, a most descriptive term used by Kussmaul and Maier [1] to describe this condition. He was emaciated, had a pinched facies, was sallow with an icteric tinge and was markedly dehydrated. Morphine in large amounts was required to control the pain in his back and abdomen. Laboratory examination at this time revealed pronounced secondary anemia, a value for

nonprotein nitrogen of 98 and an icteric index of 61. The urine gave a 3 plus reaction for albumin. It contained a few hyaline casts, many white blood cells and a few red blood cells. The blood pressure rose to 154 systolic and 110 diastolic. The jaundice rapidly increased, and bilateral parotitis developed. He died on October 10, seven months after the onset of symptoms.

At necropsy there were observed multiple infarcts of the kidneys and liver. There were recent and old ulcers of the gastrointestinal tract, the jejunum presenting a penetrating ulcer with localized acute fibrinous peritonitis. The large intestine disclosed an acute and subacute hemorrhagic type of ulcerative colitis incident to the vascular abnormalities. The heart was hypertrophied and dilated and presented many recent as well as old myocardial infarcts, a recent infarct of the wall of the right auricle, acute diffuse hemorrhagic pericarditis and mural thrombosis of the left auricular and ventricular chambers. There were multiple recent emboli in the branches of the pulmonary arteries, with infarction of the parenchyma of the lung. The adrenal glands and testicles presented evidence of recent hemorrhage. The characteristic lesions of periarteritis nodosa were demonstrated in the coronary, gastrointestinal, mesenteric, renal and hepatic arteries (fig. 3).

COMMENT

In the pre-Wassermann era this disease process was thought to be syphilitic in origin, most likely because of the tendency to aneurysm formation. Patients whose cases have been reported since that time, however, have shown no higher percentage of positive Wassermann reactions than have a similar group unaffected by this disease. Recent or prodromal infections the convalescence of which seems to merge with the onset of this disease have been reported in more than half the cases. In Spiegel's [2] report on 17 patients, 7 had prodromal infections immediately preceding the onset of symptoms, and 2 had had preceding atypical scarlet fever within two months. The hemolytic streptococcus is the organism most frequently associated with the prodromal infection. The disease has been known to occur at all ages from infancy to senescence. More than 50 per cent of the patients, however, are in the age group between 20 and 40. Males are more frequently affected; there were 4 males to 1 female in Gruber's [3] series of 113 patients.

The disease is typically chronic and progressive, lasting a few weeks or at most a few months. The symptoms are amazingly variegated and fleeting, the first ones being referable to the system or viscera whose arteries are first affected. Frequently, one set of symptoms may improve or entirely subside as the lesions in the vessels heal and their lumens recanalize or as collateral circulation develops, only to be followed or overlapped by an entirely new symptom complex. In many cases an erroneous diagnosis of "surgical abdomen" is made. Seven of

2. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

3. Gruber, G. B.: Zur Frage der Periarteritis nodosa, Virchows Arch. f. path. Anat. **258**:441, 1925.

Spiegel's [2] patients were treated with celiotomy, the diagnosis of appendicitis having been made preoperatively in 5 instances. When the viscera of the upper part of the abdomen are involved, a diagnosis of cholecystitis or pancreatitis is often made. Singer [4] reported the cases of 2 patients, 1 of whom was subjected to cholecystectomy, while the other escaped the same operation because of unexplained delirium. Penetrating ulcers of the intestinal tract resulting from infarction of the wall of the intestine are common. The early and almost constant involvement of the renal arteries causes pain in the back radiating into the flanks and abdomen. This phenomenon is well demonstrated in the present case. Earlier reports indicated that this disease always resulted fatally, most likely because it was usually reported by the pathologists. The more recent literature indicates that in about 10 per cent of cases the patient may recover or the disease become arrested for long periods.

SUMMARY

A case is reported in which the patient was operated on for a penetrating peptic ulcer, the exploration revealing no evidence of ulcer but an apparently chronic cholecystitis. A cholecystectomy and an appendectomy were performed, and material for biopsy was removed from the liver. Pathologic examination of the specimens revealed the changes in the gallbladder to be due to a disease of the blood vessels supplying it, namely, periarteritis nodosa. The outstanding clinical and pathologic features of the disease are discussed. Emphasis is placed on the frequency with which periarteritis nodosa is incorrectly diagnosed as a lesion requiring surgical intervention.

116 East Fifty-Eighth Street.

4. Singer, H.: Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations: Report of Two Cases, Arch. Int. Med. **39**:865 (June) 1927.

PERIPHERAL VASOSPASM FROM TOBACCO

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Tobacco, regardless of its form or the manner in which it is used, produces peripheral vasospasm.

The earliest use of tobacco and toxicologically allied plants by man antedates written records. Its introduction to Europe was concomitant with Columbus' second voyage to America, and the ecclesiastic Fra Romano Pane is credited with the act. He was the first to describe the effects of smoking the plant. These, as he observed them, were a quieting influence, the production of pleasant dreams and the transport of the smoker to another world. He also recognized the variation in strength of different tobaccos.

Little was known concerning the principles responsible for the general effects of using tobacco until its chief alkaloid, nicotine, was isolated by Posselt and Reimann at Heidelberg, Germany, in 1828. This discovery may be considered the basis for most of the subsequent experimental work on tobacco, and the pharmacologic and toxicologic character of the plant is, for practical purposes, solely that of nicotine.[1] The fact that the leaf is smoked, however, introduces the possibility that intermediary products of combustion are in part responsible for the physiologic changes associated with the act.

Tobacco smoke has been shown by Lee [2] and later by Dixon [3] to contain as its main constituents nicotine, pyridine bases, carbon monoxide and ammonia; in addition, traces of cyanides and sulfocyanates are found. The substances readily absorbed by the body are nicotine and carbon monoxide, and they are therefore the only elements capable of producing general physiologic effects. The others are of interest solely

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Aided by a grant from the James and Elizabeth Inglis Fund for Surgery Research.

1. Cushny, A. R.: A Text-Book of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1936, p. 464. Sollmann, T. H.: A Manual of Pharmacology, and Its Applications to Therapeutics and Toxicology, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 406.
2. Lee, E.: Quart. J. Exper. Physiol. **1**:35, 1908.
3. Dixon, W. E.: Brit. M. J. **2**:719, 1927.

because of their local irritative propensities and are held responsible for the conjunctivitis, morning cough and irritation of the mouth and tongue frequently experienced by heavy smokers and by frequenters of smoke-filled rooms.

The amount of carbon monoxide in tobacco smoke in general varies directly with the diameter of the smoking surface and the moisture present. Baumberger [4] stated that as cigaret smoke reaches the mouth it may contain as much as 7.2 to 25 parts of carbon monoxide in 10,000 parts of air. Theoretically, with continuous smoking of cigarets for one hour at five puffs per minute, the blood of the smoker might be 22 per cent saturated with carbon monoxide. Practically, however, Rühl and Lin [5] found that the highest point of saturation of the blood actually reached in inhalers is between 1 and 2 volumes per cent, the average being but 0.52 volumes per cent. This degree of saturation cannot be of physiologic significance except at very high altitudes. Thus, any general physiologic effect that is consistently observed to be associated with the use of tobacco can, with only slight reservation, be ascribed to nicotine. The nicotine actually absorbed in smoking or chewing varies with the variety of tobacco used.[6] The form in which the tobacco is smoked also determines the amount of nicotine available for absorption, the largest amounts per unit of weight being obtained from cigars and pipes and the smallest from cigarets. This result is due to the more nearly complete combustion of the nicotine in the cigaret. Also, the drier the tobacco smoked, the better the combustion and the smaller the nicotine content of the smoke. Baumberger [4] found that on an average 0.573 per cent of the cigaret by weight appears as nicotine in the smoke. Since the weight of a cigaret is approximately 1 Gm., about 3.878 mg. of the alkaloid is taken into the oronasal and respiratory passages; the amount actually absorbed, however, Baumberger concluded, is less, since absorption is not complete and only 66.7 per cent, or 2.52 mg., is assimilated by a noninhaler and 88.2 per cent, or 3.33 mg., by an inhaler. Maddock and Coller [7] found that 1 mg. constitutes an adequate stimulus when administered intravenously to the human subject.

There can be little doubt, therefore, that the smoking of one cigaret provides an amount of nicotine sufficient to account for the vascular reactions to be ascribed to tobacco. Certain experimental controls will be described as proof positive of this contention.

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4. Baumberger, J. P.: J. Pharmacol. & Exper. Therap. **21**:23, 35 and 47, 1923.

5. Rühl, A., and Lin, P.: Deutsche med. Wchnschr. **62**:493, 1936.

6. Wright, I. S., and Moffat, D.: Effects of Tobacco on the Peripheral Vascular System: Further Studies, J. A. M. A. **103**:318 (Aug. 4) 1934.

7. Maddock, W. G., and Coller, F. A.: Ann. Surg. **98**:70, 1933.

Voluminous studies by many workers on the pharmacology of nicotine have shown that it is very complicated. The drug has three sites of action, namely, the central nervous system, all the ganglions of the autonomic nervous system (thoracolumbar and craniosacral) and the nerve ends of voluntary muscle, at which it produces primary stimulation followed by paralysis. The amount of the drug needed to produce the latter effect is large and is not obtained by smoking. The vascular reaction may be elicited by action of the drug on the vasomotor center as well as on the ganglions of the sympathetic and parasympathetic nervous systems. Vasomotor reactions to smoking may, in general, be considered the result of stimulation of the cells of the central and of the sympathetic nervous system. Euzière and his associates [8] suggested an additional mechanism of action, that of sensitization of sympathetic reflex mechanisms to adequate stimuli.

Actual experimental work on the effect of smoking on the peripheral vascular reactions of man was begun by Bruce and his associates [9] in 1909, when they demonstrated the peripheral vasoconstrictor action of tobacco by means of the plethysmograph. Simici and Marcu [10] and also Ralli and Oppenheimer [11] later carried out the same sort of studies. No publication, however, made reference to this important work in a consideration of the apparent relation of tobacco and thromboangiitis obliterans until that of Maddock and Coller [7] in 1933. Experimental work by them with cutaneous temperatures used to show the peripheral vasoconstrictor effect of tobacco, although it did not demonstrate any casual relation between tobacco and thromboangiitis obliterans, firmly established the important therapeutic principle that no tobacco should be allowed persons with this disease. This principle had been previously laid down independently by Buerger,[12] Silbert [13] and Samuels [14] on the basis of clinical observations.

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8. Euzière, J.; Castagné, R; Lafon, R., and Benedittini, A. J.: Bull. Acad. de méd., Paris **116**:615, 1936.

9. Bruce, J. W.; Miller, J., and Hooker, D.: Am. J. Physiol. **24**:104, 1909.

10. Simici, D., and Marcu, Q.: J. de physiol. et de path. gén. **25**:57, 1927.

11. Ralli, E. P., and Oppenheimer, B. S.: Proc. Soc. Exper. Biol. & Med. **26**:9, 1928.

12. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

13. Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): Results of Treatment with Repeated Injections of Hypertonic Salt Solution, J. A. M. A. **94**:1730 (May 31) 1930.

14. Samuels, S. S.: Treatment of Gangrene Due to Thrombo-Angiitis Obliterans, J. A. M. A. **96**:751 (March 7) 1931.

The experimental findings of Maddock and Coller [7] have since been substantiated and extended by Barker,[15] Wright and Moffat [6] and Lampson [16] in the United States and by Euzière abroad.

The experimental work reported in this paper was performed at the University of Michigan Hospital. The effect of smoking on the vascular system of normal subjects was first investigated. Environmental factors were well controlled, the room temperature being maintained between 25 and 28 C. in order to make sure that peripheral vasospasm was not present to any great degree at the beginning of the experiment. An electric fan, running at low speed, provided a constant circulation of air. Psychic stimuli were eliminated as well as possible by insistence on quiet and recumbency of the subject for one hour prior to any observations.

Determinations of cutaneous temperature with the (Tycos dermatherm) of the palmar surfaces of the fingers and the plantar surfaces of the toes and pressure and pulse readings were made at intervals of five minutes throughout the experiment. Tobacco was withheld for a sufficient period to establish the fact that an essentially steady state existed. The subject was then given his usual form of tobacco to smoke in his usual manner. Observations were continued after completion of the act of smoking until definite recovery had ensued. Twenty subjects, including both "light" and "heavy" smokers, were observed. In all cases a progressive decrease in cutaneous temperature of the extremities and an increase in blood pressure and pulse rate occurred shortly after the beginning of smoking and persisted after cessation. For some subjects oral and truncal temperatures were recorded; these showed no change. The recovery period was of varying length in different instances; in none was it less than five or more than seventy minutes. Interestingly, it was found that the temperature of the fingers returned to normal more rapidly than did that of the toes, the difference being as much as three minutes in some cases. When a second cigaret was smoked after recovery, the changes just described occurred in parallel degree. Chart 1 illustrates graphically a typical result. The extent of the reaction and the time necessary for recording are apparent. No significant consistent variation in the responses of "heavy" and those of "light" smokers could be established.

It was recognized during these experiments that factors other than nicotine might have been responsible for the phenomena noted. The possibility that the altered rate, rhythm and depth of breathing incident to smoking might produce the changes was first investigated. The subject

15. Barker, N. W.: Proc. Staff Meet., Mayo Clin. **6**:65, 1931.

16. Lampson, R. S.: Quantitative Study of Vasoconstriction Induced by Smoking, J. A. M. A. **104**:1963 (June 1) 1935.

was given a small paper tube or an empty pipe and instructed to carry out smoking movements, simulating as nearly as possible actual smoking. Negligible changes in pulse rate, blood pressure and cutaneous temperature occurred. Mulinos and Shulman [17] have since reported peripheral vasoconstriction in the hand associated with deep breathing, but we feel that this played no role in the experiments cited here. The possibility that carbon monoxide or other products of incomplete combustion of organic matter might have played a part was ruled out when no vascular response could be elicited by smoking cubeb cigarets. Wright and Moffat [6] have made the same observation, using ashless filter paper cigarets.

A third group of control experiments was conducted, in which the smoke was first passed through two water bottles or through a layer

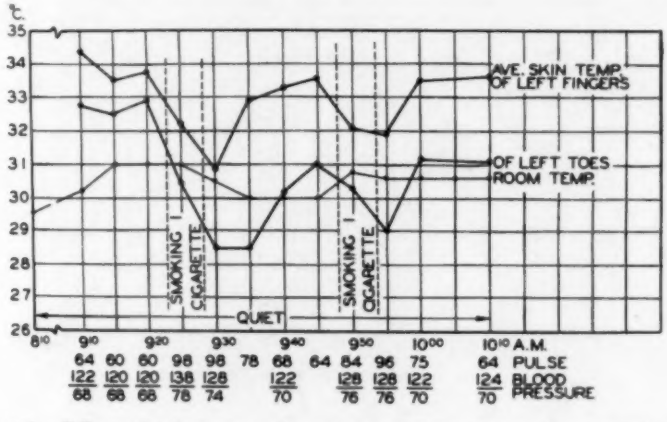

Chart 1.—Effect of tobacco on the cutaneous temperature of a normal subject.

of cotton impregnated with ferric chloride, both of which act as filters. The same cardiovascular changes occurred, but to a lesser degree.

Two cases of unquestionable thromboangiitis obliterans were then investigated. In both there was marked reduction of the cutaneous temperature of the toes when a cigaret was smoked. In 1 case, illustrated in chart 2, there was a marked difference in clinical signs of vascular deficiency between the two legs, the left having only feeble pedal and popliteal pulses and the right having a fair arterial thrust in the corresponding locations; nevertheless, there was a definite drop in the temperature of the foot with the far advanced arterial change. Lampson [16] has verified these findings. A similar response to smoking has been described by Blotner [18] in the case of a young man with

17. Mulinos, M. G., and Shulman, I.: Am. J. Physiol. **125**:310, 1939.
18. Blotner, H.: Ann. Int. Med. **9**:987, 1936.

diabetes and arteriosclerotic gangrene, the diagnosis being subsequently verified pathologically. One cannot assume, therefore, if clinically the great vessels are sclerotic, that the arterioles and capillaries are incapable of vasomotor changes; thus, as will be reiterated, tobacco is harmful to all persons with peripheral vascular deficiency without regard to age or to the status of the large vessels.

Fairly direct proof that nicotine absorbed in the act of smoking is the principle activating the vasospastic response was obtained by a fourth series of experiments, in which nicotine was administered intravenously. In a small group, nicotine hydrochloride given orally in doses of 1 mg. in 30 cc. of water, repeated every ten minutes for one hour, failed to produce any toxic effects. No cardiovascular response was noted. It was therefore deemed safe to administer intravenously 1 mg.

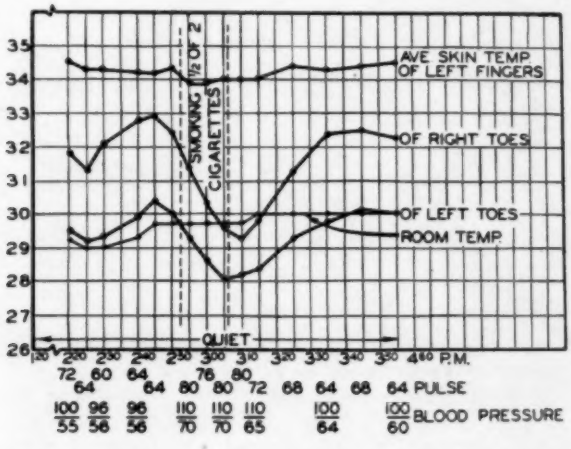

Chart 2.—Effect of tobacco on the cutaneous temperature of a subject with thromboangiitis obliterans.

in the form of the tartrate or alkaloid. A solution was made up, 1 cc. of saline solution containing 0.1 mg. of the drug. The vasomotor reactions incident to pain and psychic stimulation associated with needling of the vein were obviated by adding a two way valve to the needle attachment of the buret. Ringer's solution was given slowly until a steady state had been reached; then 10 cc. of saline solution was injected, without response, and was followed by Ringer's solution, which in turn was followed by the saline-nicotine solution. Ringer's solution was thereafter administered to the end of the observation period. Chart 3 fully illustrates the cardiovascular response obtained in this manner. There occurred, to a remarkably comparable degree, all the changes noted with the smoking of one cigaret.

The failure of large doses of nicotine administered by mouth to induce vascular responses can be explained only on the assumption

that in no given interval was there present in the general circulation an amount of alkaloid sufficient to constitute a threshold stimulus, and this may be either partly or largely due to relative slowness of absorption by the gastrointestinal tract.

The question may well arise how an amount sufficient for a threshold stimulus can be absorbed by the mucous membranes of the mouth of a noninhaler, since the surface area and absorptive powers of the mucous membranes of the mouth are less than those of the gastrointestinal tract proper. The answer may be that the nicotine in smoke, being in a finely divided state, is far more easily assimilable than that in actual solution in water. An alternative explanation previously advanced,

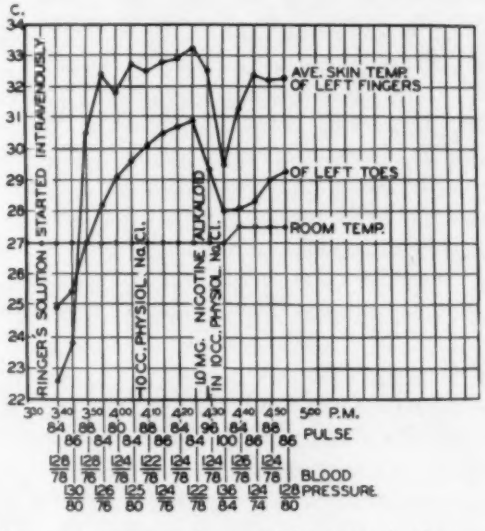

Chart 3.—Effect of intravenously administered nicotine on the cutaneous temperature of a normal subject.

based on the work of Biebl and his associates,[19] is that when absorbed from the main gastrointestinal tract the substance is detoxified by the liver before it reaches the general circulation. However, recently Helmer and his associates [20] have succeeded in isolating nicotine from the urine of smokers in considerable amounts, the drug being present three to four days after the last smoke. Thus, not all the nicotine ingested could be so rapidly detoxified when given by mouth as to constitute the sole reason for the lack of response.

The fact that tobacco, by virtue of its nicotine content, produces peripheral vasospasm has thus been firmly established. This vasospasm

19. Biebl, M.; Essex, H. E., and Mann, F. C.: Am. J. Physiol. **100**:167, 1932.

20. Helmer, O. M.; Kohlstaedt, K. G., and Page, I. H.: Am. Heart J. **17**:15, 1939.

is associated with a decreased volume flow, as has been shown by the direct experiments of Lampson,[16] Wright and Moffat[6] and Euzière. The action in man is evidently mediated through the sympathetic nervous system, as has been shown by Maddock and his associates.[7] Experiments conducted on a person on whom a cervicodorsal ramisection and ganglionectomy and a lumbar ganglionectomy for Raynaud's disease had been performed, abolishing the "sympathetic nervous control" to the extremities, showed the usual responses of the blood pressure and pulse to smoking, without any changes in cutaneous temperature of the extremities. Posterior tibial nerve block also prevented the vasospastic response in the temporarily enervated extremities of normal subjects, proving that the action is not peripheral. Whether or not the vasomotor center and the peripheral sympathetic ganglions are differentially stimulated in man has not been determined.

The role which the use of tobacco plays in the origin and clinical course of the peripheral vascular deficiencies may now be briefly considered. Tobacco has been indicted by many as the inciting cause of thromboangiitis obliterans, without actual proof. Erb[21] and later Silbert[13] maintained that it is responsible. Silbert stated that there had been, as far as he knew, no fully authenticated case of Buerger's disease in a nonsmoker. In over 1,000 cases which he observed there was not 1 patient who did not smoke. As to the effect of smoking on the course of the disease, it is general knowledge that continued smoking is associated with progressive circulatory deficiency in spite of the application of all known medical aids. Silbert stated that he had never seen a recurrence of the disease once it had been arrested by treatment unless the patient resumed smoking.

The manner in which tobacco is capable of inducing the pathologic process, if it actually is able to do so, is not known. Much work has been done on sensitization to tobacco in an attempt to solve the problem.

Harkavy and his associates[22] and Sulzberger and Feit[23] have gone into the problem extensively. They concluded that a large percentage of persons suffering from Buerger's disease belong to the category of allergic persons and that the allergy is manifest to tobacco.[22] Sulzberger and Feit[23] stated that thromboangiitis obliterans must be classified as "a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco, but without any demonstrable connection with asthma." Nicotine-free extracts gave the reactions, whereas nicotine itself did not give a single unequivocal

21. Erb, W.: München. med. Wchnschr. **51**:905, 1904.

22. Harkavy, J.; Hebald, S., and Silbert, S.: Proc. Soc. Exper. Biol. & Med. **30**:104, 1932.

23. Sulzberger, M. B., and Feit, E.: J. Immunol. **24**:425, 1933.

reaction. Maddock and his associates,[24] could not demonstrate any parallelism between the hypersensitiveness to tobacco extracts and the degree of vascular response to smoking. The question whether sensitization to tobacco is the prime factor in the causation of thromboangiitis obliterans is still open.

The possibility that chronic vasospasm incident to the use of tobacco for long periods may in itself be highly important etiologically has likewise been neither proved nor disapproved. It is known, however, that drugs unallied in structure to nicotine, namely, ergot [25] and posterior pituitary,[26] are capable of producing peripheral gangrene; thus it is conceivable that nicotine may occasionally do likewise. It is also possible that chronic vasospasm may simply be a strong contributing factor to the pathologic process which is maintained by some to be due to specific endarteritis. This may well represent the actual role of tobacco in the causation of thromboangiitis obliterans.

Whether or not an actual causal relation between tobacco and thromboangiitis obliterans can ever be established, it is an absolute necessity in the management of this disease to avoid the use of tobacco completely. The primary aim in the therapy of any acute peripheral vascular deficiency is to maintain a volume flow of blood sufficient to support metabolic processes in the diseased member until a collateral circulation can be sufficiently established to permit useful function. Obviously any drug as active as nicotine in producing a decreased blood flow in the extremities must be assiduously avoided, or treatment is useless. One might well say "Your legs or your cigarets" and refuse to treat any patient with thromboangiitis obliterans who continues to smoke. For the elderly person with arteriosclerotic peripheral vascular deficiency it is often difficult to stop smoking entirely, but it is desirable to reduce the use of tobacco as much as possible.

The use of patented filters and the so-called denicotinized cigarets must likewise be prohibited, as there is at present voluminous proof that the filtering and denicotinizing processes are not adequate to prevent the vasospasm associated with smoking.[27]

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24. Maddock, W. G.; Malcolm, R. L., and Coller, F. A.: Am. Heart J. **12**: 46, 1936.

25. Jablons, B.: Internat. Clin. **3**:193, 1925.

26. Holsclaw, F. M., and Booth, J. A.: Arch. Pediat. **42**:64, 1925.

27. Segal, H. L.: Am. J. M. Sc. **196**:851, 1938. Wright and Moffat.[6] Maddock and Coller.[7] Lampson.[16]

SURGICAL INTERVENTION ON THE SYMPATHETIC NERVOUS SYSTEM FOR PERIPHERAL VASCULAR DISEASE

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Since the work of Royle and that of Hunter [1] on the relation between the sympathetic nervous system and spastic paralysis, it has become obvious that a striking and persistent increase in blood flow follows interruption of sympathetic pathways to the extremities. Although previous attempts to increase peripheral blood flow by periarterial sympathectomy [2] had been followed by transient improvement, lumbar ramisectomy as practiced by Royle [3] and by Hunter [1] resulted in a more prolonged effect. This observation was the stimulus for extensive study of the relation between the sympathetic nervous system and the peripheral circulation. During the past fifteen years much has been learned about the anatomy and physiology of the sympathetic nervous system.[4] Clinical application of this knowledge to the treatment of various peripheral vascular disorders now appears to be well established.

FUNDAMENTAL PRINCIPLES

Out of the tremendous amount of clinical and experimental evidence collected in the past decade has emerged the fact that certain fundamental principles must be observed in order to get the best clinical results. First, it seems clear that an operation to be successful must

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1. Hunter, J. I.: The Influence of the Sympathetic Nervous System in the Genesis of the Rigidity of Striated Muscle in Spastic Paralysis, Surg., Gynec. & Obst. **39**:721, 1924.

2. Leriche, R.: De l'élongation et de la section des nerfs périvasculaires dans certains syndromes douloureux d'origine artérielle et dans quelques troubles trophiques, Lyon chir. **10**:378, 1913.

3. Royle, N. D.: A New Operative Procedure in the Treatment of Spastic Paralysis and Its Experimental Basis, M. J. Australia **1**:77, 1924.

4. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, Baltimore, William Wood & Company, 1934. Livingston, W. K.: The Clinical Aspects of Visceral Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

be thorough in its interruption of sympathetic motor fibers to the part in question. Second, an operation on the sympathetic nervous system must interrupt either preganglionic or postganglionic pathways or a combination of the two. The best results have been obtained by interruption, as far as possible, of preganglionic fibers only. In the third place, time has demonstrated conclusively the tremendous regenerative power of interrupted sympathetic nerves. In order to give satisfactory late results, an operation must be done in such a way as to eliminate or minimize the possibility of regeneration. Space does not permit a summary of the evidence at hand, but adequate reference is made to articles dealing with these matters.[5]

CASES IN WHICH SYMPATHECTOMY IS INDICATED

If in a given case impaired blood flow to the extremity is entirely a question of vascular spasm, as in the early stages of Raynaud's disease, sympathectomy will yield its most brilliant result. By contrast, if the vascular insufficiency is the result of chronic obliterative vascular disease, as in advanced arteriosclerosis with associated diabetes, sympathectomy will not be helpful. Many patients, however, suffer from a lesion which is both obliterative and vasospastic, in which case sympathectomy may be helpful. Thromboangiitis obliterans is representative of such a lesion.

Although the primary effect of sympathectomy is probably largely the result of vasomotor paralysis, another factor must be considered. Sympathectomy results in sudomotor paralysis in addition to vasomotor paralysis. A portion of the effect on the periphery is therefore due to inactivation of the sweat glands.

It becomes clear, then, that studies which enable one to evaluate the vasomotor and sudomotor components in a given case are of primary importance. By their use one can best predict the effect of operation.

5. (*a*) Elliott, T. R.: The Action of Adrenaline, J. Physiol. **32**:401, 1905. (*b*) Cannon, W. B., and Uridil, J. E.: Studies on the Conditions of Activity in Endocrine Glands: VIII. Some Effects on the Denervated Heart of Stimulating the Nerves of the Liver, Am. J. Physiol. **58**:353, 1921. (*c*) Cannon, W. B., and Rosenblueth, A.: Studies on Conditions of Activity in Endocrine Organs: XXIX. Sympathin E and Sympathin I, ibid. **104**:557, 1933. (*d*) Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia, ibid. **107**:529, 1934. (*e*) Smithwick, R. H.; Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause of Failure of Operations for Raynaud's Disease, Arch. Surg. **29**:759 (Nov.) 1934. (*f*) Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys, Brit. J. Surg. **24**:787, 1937.

Such tests are also important in evaluating the result of operation in regard to both completeness and permanence. Those more useful and most commonly employed will be considered.

CONDITIONS FOR STUDY

The relation between the surface temperature of an extremity and the room temperature is important. Cold is a great stimulus to peripheral vasoconstriction. Pain and emotion may also be utilized, but changes in temperature are better controlled. The optimum room temperature for use in clinical studies is approximately 68 F. This should be relatively constant during the period of observation, and for this reason a "constant temperature room" with controlled humidity is desirable. It is not, however, absolutely essential. Much of clinical value can be learned without it.

It is characteristic of a vasospastic disorder that the surface temperature of a finger tip or a toe tip will be slightly lower than the room temperature if sufficient time is allowed for adjustment to take place. When obliterative vascular disease predominates, the extremity does not, as a rule, cool quite to room temperature and rarely falls below it.

When the surface temperature has become stabilized in relation to the room temperature, one can utilize a number of indirect methods of estimating the increase in blood flow. After inhibition of vasoconstriction, the resulting increase of surface temperature under conditions of constant room temperature can be measured with a thermocouple or, better, by a potentiometer indicator.

METHODS OF STUDYING VASOMOTOR ACTIVITY

Vasoconstriction can be reflexly inhibited by warming the trunk[6] or by immersion of the opposite extremities in warm water.[7] Vasoconstriction can also be inhibited by induction of fever by intravenous injection of foreign protein (typhoid vaccine).[8] The resulting rise in

6. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

7. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019, 1932.

8. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87**:379 (Aug. 7) 1926. Allen, A. W., and Smithwick, R. H.: Use of Foreign Protein in the Treatment of Peripheral Vascular Diseases: Results of Intravenous Injections of Typhoid Vaccine, ibid. **91**:1161 (Oct. 20) 1928.

surface temperature of the extremity makes it possible to estimate the vasomotor index. All three of these methods have been used extensively.

Vasoconstriction can be eliminated also by blocking the efferent vasomotor pathway with procaine hydrochloride. This test perhaps provides a better index of the result to be expected from sympathectomy, because the sudomotor pathway is also temporarily interrupted. Although paravertebral block of the sympathetic supply to the arm and leg with procaine hydrochloride is an excellent method, peripheral nerve block is more practical, almost as accurate and far easier for the average person to perform.[9]

Thus, for the hand the ulnar nerve is most frequently blocked at the elbow. This results in almost maximal vasodilation in the anesthetic area. Injection of the anesthetic into the median and radial nerves as well may result in a slight further increase in surface temperature, but not enough to make the procedure necessary in a routine test.

The foot may be temporarily denervated by block of the posterior tibial nerve at the ankle and the common peroneal nerve just below the head of the fibula with procaine hydrochloride. Injection of the anesthetic into the sciatic nerve in the gluteal region may be utilized as an alternative method. Spinal anesthesia is a satisfactory but slightly more dangerous method of causing temporary inhibition of vasoconstriction in the lower extremity.

In all of the tests mentioned so far, the increase in blood flow is indirectly measured by the rise in surface temperature of the tip of a finger or of a toe. In the presence of purely vasospastic disorders this increase will amount to as much as 25 degrees (F.). If obliterative vascular disease is the predominating factor, there may be little or no rise in surface temperature. If a combination of spasm and obliteration exists, changes in temperature of from 5 to 15 degrees (F.) are commonly seen.

Other indirect methods of estimating increased blood flow after inhibition of sympathetic influence are utilized. The finger or toe plethysmograph is a satisfactory and sensitive apparatus.[10] Hand and

9. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities with Procaine, J. A. M. A. **94**:1382 (May 3) 1930; Diagnostic Novocaine Block of the Sensory and Sympathetic Nerves: A Method of Estimating the Results Which Can Be Obtained by Their Permanent Interruption, Am. J. Surg. **9**: 264, 1930. Morton, J. J., and Scott, W. J. M.: Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Disease, New England J. Med. **204**:955, 1931.

10. Bolton, B.; Carmichael, E. A., and Stürup, G.: Vasoconstriction Following Deep Inspiration, J. Physiol. **86**:83, 1936.

foot calorimeters may be used.[11] Their use is too complicated, however, for the average clinician.

Changes in blood flow may also be quantitated by the hand plethysmograph. By this instrument the volume of blood flow per minute per unit of tissue volume may be measured fairly accurately under varying conditions. The method has been described by Freeman,[12] who has used it effectively. Much experience is required to use and interpret the results of this test correctly.

The photoelectric cell offers a sensitive method[13] of studying the effect of vasoconstriction. Instead of cooling the extremity, one places the patient in a warm atmosphere, which is conducive to vasodilation. The level of blood flow through a translucent portion of the finger tip is recorded photographically, and the reflex vasoconstrictor response is then determined. Various stimuli may be used, such as a deep breath, immersion of the opposite hand in ice water, sudden noise or an unpleasant suggestion. Many extremities have been tested for me by Finesinger[14] both before and after various operative procedures (fig. 1). The test has proved invaluable not only in estimating the effect of the intact sympathetic system on peripheral blood flow but in testing the completeness of interruption of the sympathetic nerve supply by various operations.

A study of cutaneous resistance[15] as an index of sweat gland activity is helpful in estimating activity of the sympathetic nervous system before and after operation (fig. 2). The level in ohms is important, but the reflex response to a stimulus, such as a sudden noise, is even more illuminating. I have found this test to be one of the most delicate and useful of all. It is helpful in studying the completeness of sympathectomy and the state of "relapse." Many records of its use have been made for me by Finesinger,[16] who has also made observations by these

11. Kegerreis, R.: Calometric Studies of the Extremities: II. Experimental Apparatus and Procedures, J. Clin. Investigation **3**:357, 1927.

12. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**:384, 1935.

13. Hertzman, A. B.: Photoelectric Plethysmography of Fingers and Toes in Man, Proc. Soc. Exper. Biol. & Med. **37**:529-534, 1937; Comparative Estimation of Blood Supply of Skin Areas from Photoelectrically Recorded Volume Pulse, ibid. **38**:562-564, 1938.

14. Finesinger, J. E.; Hensner, A. P., and Smithwick, R. H.: Vasomotor Studies in Raynaud's Disease Before and After Sympathectomy, Tr. Am. Neurol. A. **65**:193, 1939.

15. Landis, C.: Electrical Phenomena of the Skin (Galvanic Skin Response), Psychol. Bull. **29**:693, 1932.

16. Finesinger, J. E.: Unpublished data.

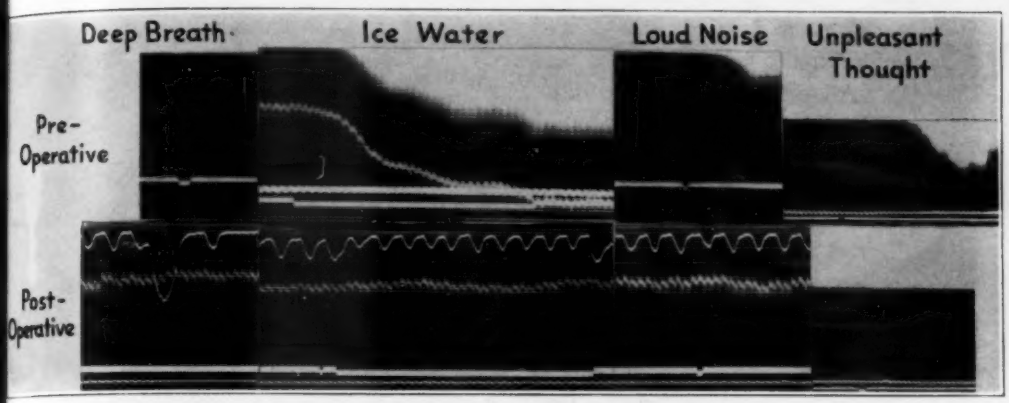

Fig. 1.—Blood flow through a translucent portion of the finger tip. Variations in blood flow are detected by the photoelectric cell, which lies beneath the finger tip, through which a beam of light passes. A fall in the blood flow level on the photograph denotes vasoconstriction; a rise, vasodilatation. The individual pulse oscillation can be seen on the records, more clearly after sympathectomy. The characteristic responses to various stimuli are shown. After a complete sympathectomy, these are abolished. Stimuli were a deep breath, a loud noise, immersion of the opposite hand in ice water and an unpleasant suggestion.

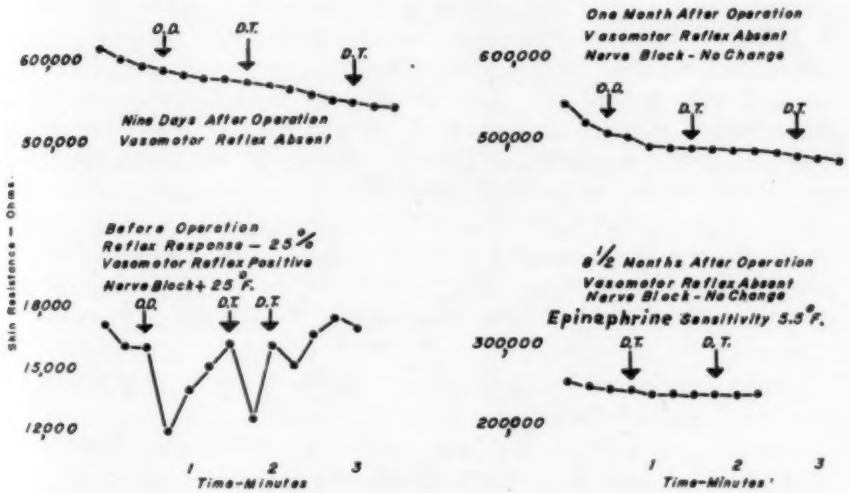

Fig. 2.—Typical record of cutaneous resistance. Before operation the level is low and variable, and a sharp fall in response to a sudden stimulus is noted. Opening the door of the room in which the patient lay or dropping a tin on the floor was the stimulus used. After a complete sympathectomy, the level of cutaneous resistance is high and constant, and reflex response is abolished. It should be noted, however, that as time goes on there is a slow fall in the level of cutaneous resistance. Because the level is not variable and reflex response is abolished, it seems most likely that this fall is due to a peripheral mechanism and is not of central origin.

methods of both vasomotor and sudomotor reflex responses in a study of normal and of psychotic persons.

All of the forms of study which have been mentioned have been utilized in this clinic. The simplest and most practical of all is peripheral nerve block; my associates and I use this routinely. Of the other tests, the study of reflex vascular response by the photoelectric cell method and the study of changes in cutaneous resistance by the Wheatstone bridge and the psychogalvanic reflex have proved most valuable. These two studies have enabled us to separate activity of the sympathetic nervous system into its vasomotor and its sudomotor components.[17]

It must be stated, however, that clinical observation and judgment must be combined with the results of the various tests in making a final decision as to the indications for sympathectomy in a given case. This applies particularly to cases in which both obliterative and vasospastic elements are present. Not uncommonly, under these circumstances, one cannot demonstrate any improvement in blood flow after interruption of sympathetic outflow by block with procaine hydrochloride. Yet one may suspect from clinical observation that a definite element of vascular spasm is present, as judged by cold, moist extremities with "multiple phase color changes." Frequently sympathectomy has resulted in a marked rise in surface temperature under these circumstances. Study of reflex vasomotor and sudomotor activity before operation will often demonstrate a marked response when there is none to peripheral nerve block. This is probably due to the fact that the latter test is carried out under conditions promoting vasoconstriction. Thus, it seems probable that a constricted arteriole with some organic change will not necessarily relax, when vasoconstriction is inhibited by procaine hydrochloride, as long as it is in a cool environment. Vasoconstriction may persist as a purely local response to cold. When, however, the same extremity is studied in a warm room, the ability of the vessels to constrict in a surprising fashion can often be demonstrated by the reflex vasomotor responses.

For this reason my associates and I routinely use both peripheral nerve block and studies of reflex vascular and sweat gland activity. As has been stated, however, the final decision for or against sympathectomy must be based on clinical judgment and experience as well as on objective tests.

CHANGES AFTER SYMPATHECTOMY

1. *When Operation is Complete.*—Interesting and characteristic changes take place after preganglionic sympathectomy. The findings vary with the time which has elapsed since operation. There seem to be

17. Darrow, C. W.: The Galvanic Skin Reflex, not a Vasoconstrictor Phenomenon, Psychol. Bull. **26**:155, 1929.

certain phases through which the extremity passes. It is therefore best to divide the discussion into three parts; namely, changes observed during the first week, changes observed during the second and third weeks, and late changes (observed months or years after operation).

(*a*) Changes During the First Week: On the day after sympathectomy, the extremity appears to be dry, warm and of excellent color. The level of surface temperature is high and would presumably not rise further on block with procaine hydrochloride. The level of cutaneous resistance is high, and reflex sweat gland activity as well as vasomotor activity is thought to be abolished. Between the third and the fifth day a curious clinical phenomenon takes place. The extremity suddenly begins to perspire, becomes cooler and often is discolored. These changes may be obvious or may be detected only by careful testing. The sudden burst of sympathetic nervous activity gradually disappears, so that by the end of a week it has vanished. During this phase there is a fall in surface temperature and in the level of cutaneous resistance. If the peripheral nerves are blocked with procaine hydrochloride during the height of the reaction, a rise in cutaneous temperature will follow. As reflex vasomotor and sudomotor activity are known to be absent during this period, it would seem that there is an actual spontaneous outflow of sympathetic impulses from the decentralized sympathetic ganglions.[18] These changes are shown in figures 3, 4 and 5.

(*b*) Changes During the Second and Third Weeks: Between the first and the second week after operation the level of cutaneous resistance reaches its high point. The surface temperature falls slowly for two or three weeks after operation; then it strikes a level.[19] The highest readings are usually obtained the first day after operation. During the second week, the phenomenon of sensitivity to epinephrine and similar substances appears. This is complete between two and three weeks after operation and is probably largely responsible for the fall in surface temperature. This matter has previously been discussed in detail.[5d, e] Thus, by the end of three weeks the extremity may be said to have become stabilized (figs. 3, 4 and 5).

18. Govaerts, J.: Contribution à l'étude de l'innervation sympathique du coeur, Arch. internat. de méd. expér. **11**:629, 1936. Tower, S. S., and Richter, C. P.: Injury and Repair Within the Sympathetic Nervous System: III. Evidence of Activity of Postganglionic Sympathetic Neurons Independent of the Central Nervous System, Arch. Neurol. & Psychiat. **28**:1149 (Nov.) 1932. Simeone, F. A.: The Effect of Regeneration of the Nerve Supply on the Sensitivity of the Denervated Nictitating Membrane to Adrenine, Am. J. Physiol. **120**:466, 1937.

19. Richter, C. P.: The Nervous Control of the Electrical Resistance of the Skin, Bull. Johns Hopkins Hosp. **45**:56, 1929.

Fig. 3.—Diagrammatic representation of the changes noted in the surface temperature level of the finger tip and in the cutaneous resistance level of the hand. It is a composite chart of the average findings in a group of denervated upper extremities as days, weeks and months passed after operation. It is presented to bring out the nature of the curve rather than the actual levels. The period of "spontaneous sympathetic activity" is shown, together with the fall in surface temperature and cutaneous resistance levels at this time. Both reflex vasomotor and sudomotor activity are abolished during this period, as after it and presumably before it.

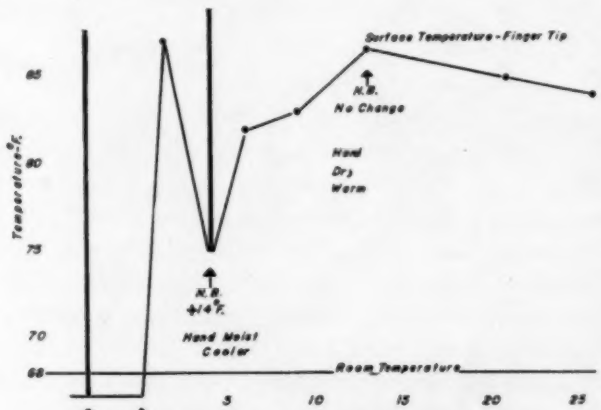

Fig. 4.—Level of surface temperature after operation on an upper extremity. It was obtained by plotting daily readings against time and room temperature. The characteristic fall in surface temperature between the third and the sixth day is shown. Block of the ulnar nerve at the low point by injection of procaine hydrochloride was followed by a sharp rise in surface temperature. This suggests that sympathetic motor impulses were passing peripherally from the decentralized ganglions, because reflex vasomotor and sudomotor responses were absent. During this phase, the hand was cool, moist and often discolored. The phenomenon disappeared, clinically at least, by the end of the first week. There was no rise in surface temperature of the finger tip when the ulnar block was repeated on the thirteenth postoperative day.

(*c*) Changes Months or Years After Operation: As the extremity is observed during the following months or years, little significant change takes place. There seems to be a slight fall in the level of surface temperature as time goes on. There is a more definite fall in that of cutaneous resistance, in spite of the fact that reflex sweat gland activity is abolished.[20] This may be due to independent activity of the sweat glands or may be a humoral response. Thus, a well sympathectomized extremity months or years after the operation should have a high surface temperature with little or no rise on block with procaine hydrochloride; a much higher level of cutaneous resistance than before operation, without evidence of reflex response, and complete abolition of reflex vasomotor activity, as evidenced by photoelectric cell studies (fig. 2).

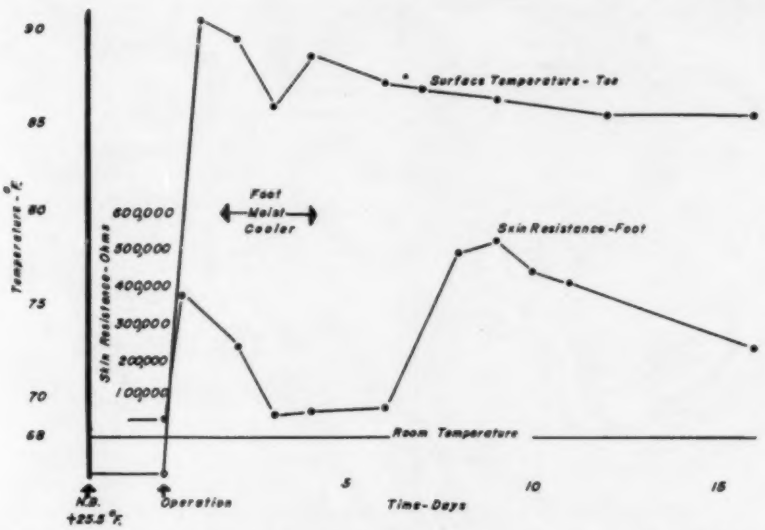

Fig. 5.—Daily surface temperature and cutaneous resistance readings, plotted for two weeks after complete denervation of the lower extremity. The curves are similar to those noted for the upper extremity. The same phase of lowered temperature and cutaneous resistance levels accompanied by clinical evidence of moisture and coolness is brought out. Note the sharp fall in cutaneous resistance during the second week. As reflex sudomotor activity is abolished completely, this cannot be utilized as evidence of either incomplete sympathectomy or regeneration. It may be some peripheral mechanism (perhaps humoral) affecting the sweat glands directly.

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20. Richter, C. P.: A Study of the Electrical Skin Resistance and the Psychogalvanic Reflex in a Case of Uni-Lateral Sweating, Brain **50**:216, 1927. Solomon, P.: The Psychogalvanic Reflex: Applications to Neurology and Psychiatry, Arch. Neurol. & Psychiat. **34**:818 (Oct.) 1935.

There should be a slight drop, of about 5 degrees (F.), in surface temperature in response to epinephrine.

Occasionally a rise of 1 to 3 degrees (F.) in surface temperature is noted on peripheral nerve block in the absence of evidence of reflex sudomotor or vasomotor activity. This may be the result of a continued slight discharge of impulses from the decentralized ganglions (fig. 6).

2. *When Operation Is Incomplete.*—There is a marked difference between the results of complete and those of incomplete interruption of sympathetic impulses to an extremity. If the operation is only partially effective, the level of surface temperature may be changed little, if any. Hence, peripheral nerve block will result in a marked rise in

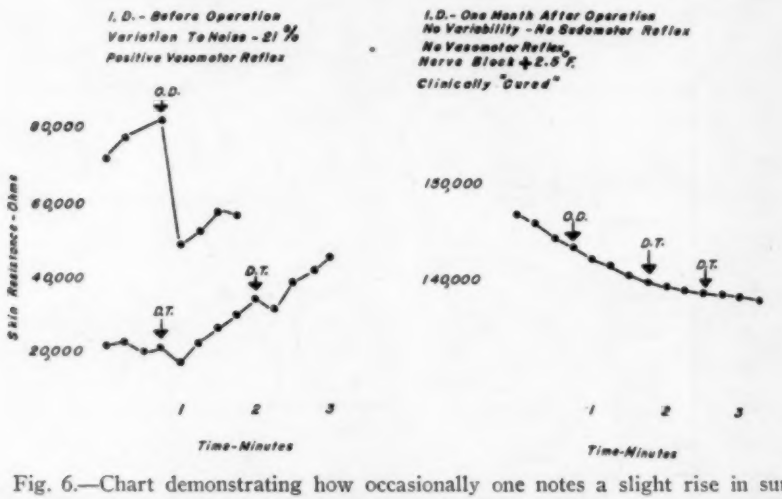

Fig. 6.—Chart demonstrating how occasionally one notes a slight rise in surface temperature of a finger tip following peripheral nerve block after an apparently complete sympathectomy, as evidenced by abolition of vasomotor and sudomotor reflexes. This chart should be compared with figure 2, which shows the usual result. This slight rise in surface temperature following peripheral nerve block is perhaps best explained by assuming persistence of some efferent sympathetic motor activity arising in the decentralized ganglions. It does not appear to be of any clinical significance.

cutaneous temperature. The level of cutaneous resistance will be low, and reflex sweat gland activity will be present. Reflex vasomotor responses will persist. Sensitivity to epinephrine will not appear. The effect of incomplete sympathectomy in terms of surface temperature is shown in figure 7. The case illustrated was very helpful to me in my early attempts to find an adequate preganglionic type of operation for the upper extremity.

3. *When "Relapse" Takes Place.*—This subject has been well discussed by Simmons and Sheehan.[21] The term as they used it is descriptive. It implies a state of affairs which occurs six months to a year and a half after what was thought to be a complete operation. It implies also that the symptoms are not quite the same as before operation. The condition occurs after both preganglionic and postganglionic types of sympathectomy. The explanation has not been wholly clear.

The patient notices that after a period of relief or improvement the extremity begins to be cooler and also to perspire. Slight changes in color may occur, but the symptom complex does not seem to be as severe as before operation. This situation is undoubtedly due to partial regen-

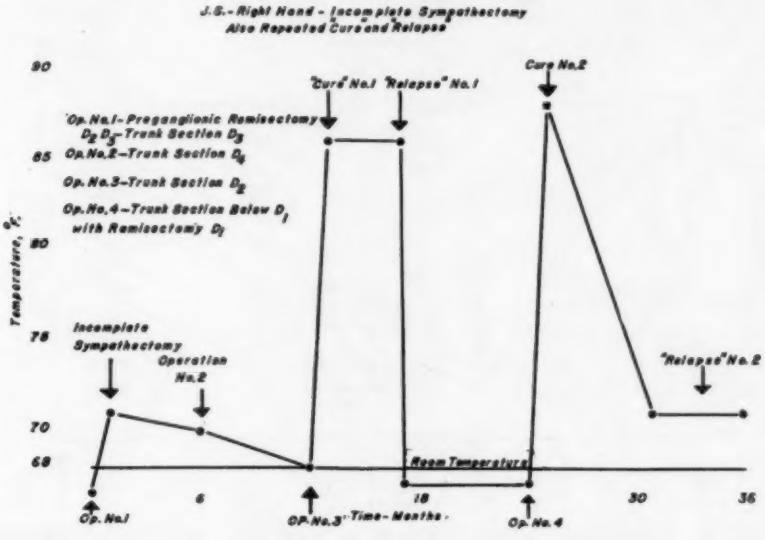

Fig. 7.—Case of J. S. The ability of a finger tip to maintain a high surface temperature level in a cool environment may be utilized in judging the completeness of sympathectomy. The first two operations failed to denervate the hand because the white rami from the second and third dorsal segments were not actually divided. This was temporarily corrected by operations 3 and 4. "Relapse" due to regeneration occurred, however, after both of these procedures.

eration of sympathetic fibers. The effect of repeated "relapse" in terms of surface temperature is shown in figure 8. The case illustrated was also extremely helpful to me in working out an operation for the upper

21. Simmons, H. T., and Sheehan, D.: An Inquiry into "Relapse" Following Sympathectomy, Lancet **2**:788, 1937.

extremity which would be adequately complete, preganglionic and not followed by regeneration or "relapse."

In most studies of the state of "relapse," reflex sweating has been used as evidence of regeneration of vasomotor fibers. I have had occasion to observe a number of extremities in which there has been a "relapse" and to study reflex sweat gland activity and reflex vascular response separately. This has been done by utilizing cutaneous resistance readings and the psychogalvanic reflex in the former and reflex photoelectric cell responses in the latter instance.

It was found (table 1) that the vasomotor reflex was absent in all of 8 "relapsed extremities" after either preganglionic or postganglionic operations.

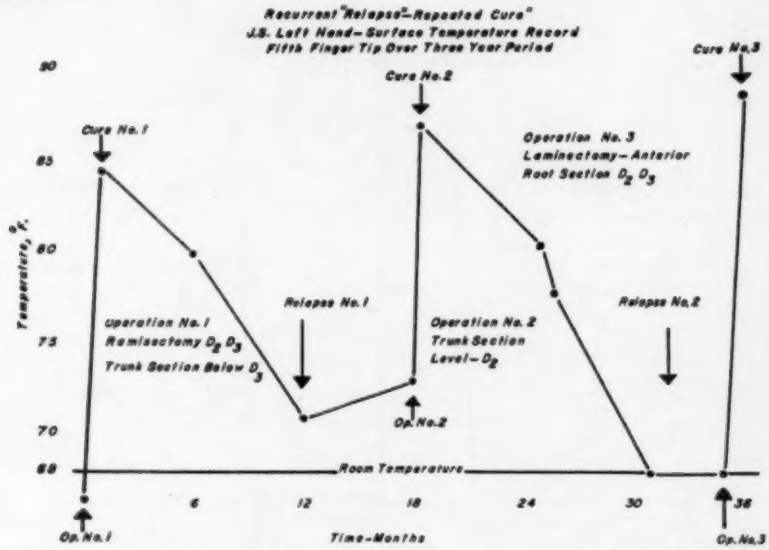

Fig. 8.—Chart indicating that section of the rami and division and displacement of the nerve trunk are not adequate assurance against regeneration in the case of the upper extremity. This upper extremity was well denervated twice, but regeneration occurred and "relapse" resulted. Several similar experiences convinced me that the anterior roots of the second and third dorsal nerves must be divided to prevent this occurrence. (See figure 11.)

In table 2, data on reflex sweat gland activity in 5 of these cases are presented. A fall in the level of cutaneous resistance in response to an adequate stimulus was present in each instance in a degree comparable to that seen in the average untreated extremity. This was true regardless of the type of operation which had been performed (fig. 9). This reflex was abolished after further surgical intervention had been undertaken to interrupt regenerated pathways (fig. 10). In table 3, other changes in the state of "relapse" are contrasted with the findings in the

TABLE 1.—*Vasomotor Activity in Eight Cases of Relapse (Upper Extremity)* *

Patient	Hand	Degree of Relapse	Operation	Time Since Operation, Mo.	Vasomotor Reflex
J. S.	Right	Mild	Ramisectomy	30	Absent
D. McG.	Left	Mild	Ramisectomy	27	Absent
J. S.	Left	Moderate to marked	Ramisectomy	30	Absent
Alves	Right	Moderate to marked	Ramisectomy	10	Absent
Alves	Left	Moderate to marked	Ramisectomy	10	Absent
A. McJ.	Left	Moderate to marked	Ramisectomy	24	Absent
A. McG.	Right	Moderate to marked	Ganglionectomy (C_2; D_1; D_2)	65	Absent
P. B.	Left	Moderate to marked	Ganglionectomy (D_1; D_2)	97	Absent

* No reflex response was demonstrated in any instance by the photoelectric cell method, regardless of the type of operation. All the operations were believed to have been originally complete.

TABLE 2.—*Reflex Sweat Gland Activity in Five Cases of "Relapse" (Upper Extremity).* *

Patient	Hand	Degree of Relapse	Operation	Time Since Operation, Mo.	Cutaneous Resistance, Ohms	Reflex Response	Vasomotor Reflex
J. S.	Right	Mild	Ramisectomy	30	125,000	8%	Absent
D. McG.	Left	Mild	Ramisectomy	27	74,000	15%	Absent
J. S.	Left	Moderate to marked	Ramisectomy	30	100,000	13%	Absent
A. McG.	Left	Mild	Ramisectomy	24	30,000	22%	Absent
A. McG.	Right	Mild	Cervicodorsal ganglionectomy	65	35,000	10%	Absent
			After Secondary Operation				
J. S.	Left	"Cured"	Laminectomy; anterior root section (D_2, D_3)	1	190,000	Absent	Absent

* No reflex vasomotor activity could be detected by the photoelectric cell method. The reflex sweat gland activity was abolished in 1 of these extremities after further operation had interrupted regenerated nerve pathways.

TABLE 3.—*Comparison of Data on a "Relapsed" and Data on a "Cured" Upper Extremity* * *After Interruption of Regenerated Sympathetic Pathways*

	Symptoms	Rise in Temperature with Ulnar Block	Fall in Temperature on Intravenous Administration of Epinephrine	Vasomotor Reflex	Cutaneous Resistance Level	Variability	Reflex
"Relapsed"	Marked	13 degrees F.	2 degrees F.	Absent	100,000	Marked	Positive, 13%
"Cured," 1 mo. after operation	None	1.8 degrees F.	8.5 degrees F.	Absent	190,000	None	Absent

* Left hand of patient J. S.

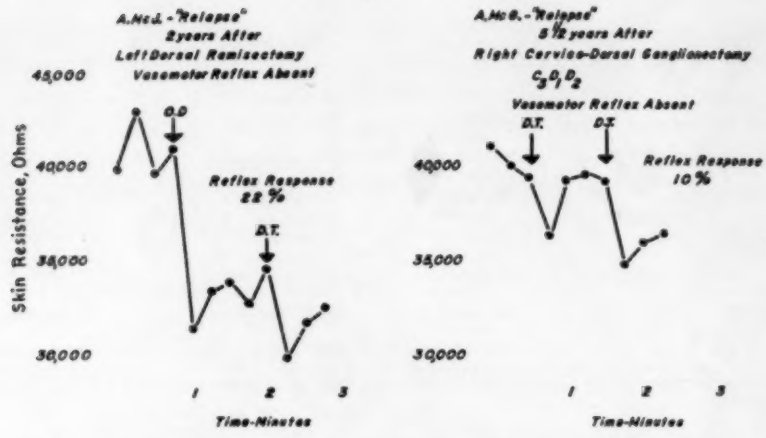

Fig. 9.—Low, variable levels of cutaneous resistance with positive reflex response years after what was believed to have been a complete denervation. In one case a preganglionic ramisectomy had been performed; in the other, a ganglionectomy. The picture represented by this chart is comparable to that seen before operations as far as changes in cutaneous resistance are concerned. Note, however, that no reflex vasomotor response was demonstrated by the photoelectric cell in either instance.

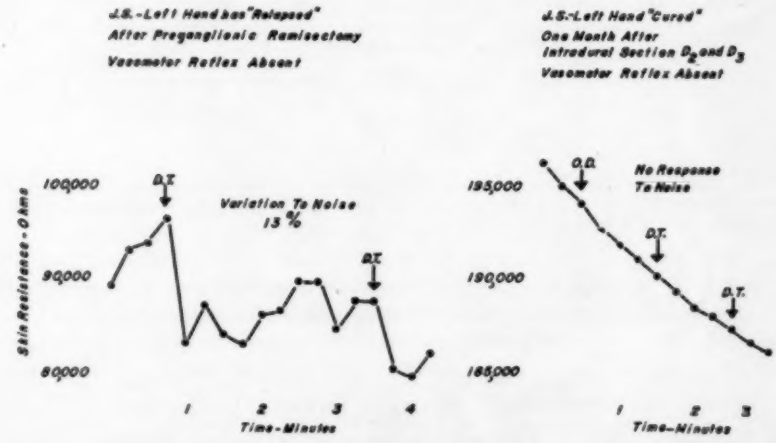

Fig. 10.—Chart showing that further operation after "relapse" results in a higher, constant level of cutaneous resistance without reflex response. The vasomotor reflex as judged by the photoelectric cell method was absent both in the "relapsed" and in the "cured" state.

same extremity after the symptoms had been completely relieved by further surgical procedures.

These observations indicate that in the state of "relapse," reflex activity of the sweat glands is present in a degree comparable to that seen when operation has not been performed. The vascular reflex, however, could not be demonstrated by the same technic (photoelectric cell) which always produced a response in the normally innervated extremity. Further study will be necessary to determine the accuracy and significance of these findings.

OPERATIVE TECHNIC

The foregoing summary of changes noticed after various operations on the sympathetic nervous system is given primarily to show why I use the type of operation to be described. The difficulties encountered apply

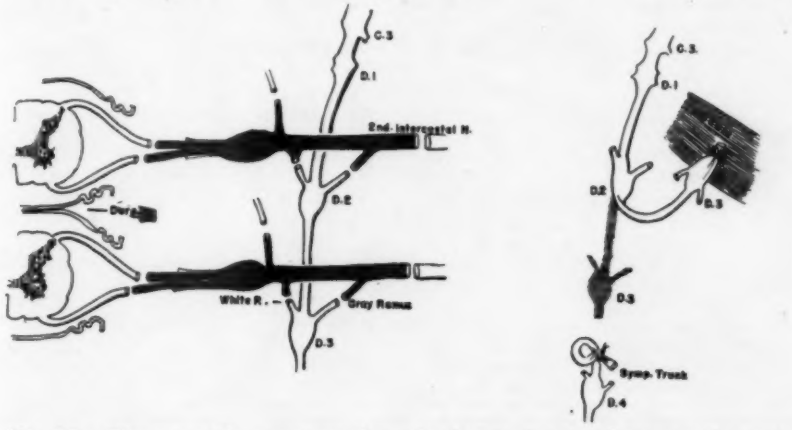

Fig. 11.—Diagrammatic representation of what is done to interrupt the sympathetic outflow from the second and third dorsal segments in order to prevent regeneration. The impulses from the lower dorsal levels are interrupted by dividing the trunk below the third dorsal ganglion and ligating the distal divided end. The proximal divided end is brought out of the thorax and sutured into the wound to prevent regeneration from this source. The outflow from the first dorsal segment is not interrupted because it is insignificant in amount and cannot be permanently abolished without sacrificing the first dorsal motor root. This would result in motor weakness in the extremity. Exposure is obtained by resecting the inner portion of the third rib and the tip of the transverse process through a small vertical paravertebral incision. The pleura is separated from the thoracic cage over an appropriate distance. See other references for more detailed description of the operation. An operation, similar in principle, utilizing an anterior approach, has been described (Telford, E. D.: The Technique of Sympathectomy, Brit. J. Surg. **23**:448, 1935).

almost wholly to the upper extremity. It never has been a problem to produce an adequate, lasting and preganglionic type of operation for the lower extremity.

These operations have been described in great detail elsewhere.[22] The operation for the arm (fig. 11) and that for the leg (fig. 12) are described briefly.

CLINICAL RESULTS

Table 4 is a summary of clinical results following sympathetic denervation of the upper extremity by the method described (root section). Also included are earlier cases in which operation (ramisectomy) was performed. The results in these cases were not as good, and this led to the development of the present technic, which appears

TABLE 4.—*Clinical Results for Upper Extremity* *

	No. of Extremities	Excellent Clinical Result	Improved	Unimproved
Group I				
All operations	33	28 (84%)	3 (10%)	2 (6%)
Ramisectomy	6	1 (17%)	3 (50%)	2 (33%)
Root section	27	27 (100%)	.....	.....
		Very Good Clinical Result	**Improved**	**Unimproved**
Group II				
All operations	34	25 (73.5%)	8 (23.5%)	1 (3%)
Ramisectomy	10	5 (50%)	4 (40%)	1 (10%)
Root section	24	20 (83.3%)	4 (16.7%)	.....
		Good Clinical Result	**Improved**	**Unimproved**
Group III				
All operations	26	12 (46%)	12 (46%)	2 (8%)
Ramisectomy	9	2 (22.5%)	5 (55%)	2 (22.5%)
Root section	17	10 (58.8%)	7 (41.2%)	.....

* The results of various types of preganglionic operations are given in this table. The best results were those following root section as illustrated in figure 11. All cases in this table are examples of primary vascular spasm. They are grouped according to the degree of local fault present before operation (see text).

satisfactory. The cases are arranged in three groups, according to the degree of local fault already present. There was no obvious local fault in the cases in group I. There were definite cutaneous changes in the extremities in group II (scleroderma), but no roentgen change. Group III contained cases of advanced scleroderma and definite roentgen changes, such as calcification of soft tissues or destruction of bone

22. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity: Preliminary Report, Ann. Surg. **104**:339, 1936; The Value of Sympathectomy in the Treatment of Vascular Disease, New England J. Med. **216**:141, 1937; The Sympathetic Nervous System and Vascular Disease, in Blumer, G.: The Practitioner's Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1938, vol. 13; The Rationale and Technique of Sympathectomy for the Relief of Vascular Spasm of the Extremities, New England J. Med., to be published.

of the terminal phalanges. The untoward effect on the end result of the degree of local fault already present is clearly shown.

Table 5 includes data on a group of cases in which the vascular spasm of the upper extremity was secondary to some underlying disease. The results in this group are comparable to those obtained in group III, table 1.

Table 6 represents a consecutive series of denervated lower extremities. The extraperitoneal approach was utilized in every instance. The cases are divided into two groups, depending on whether the vasospasm was primary or secondary.

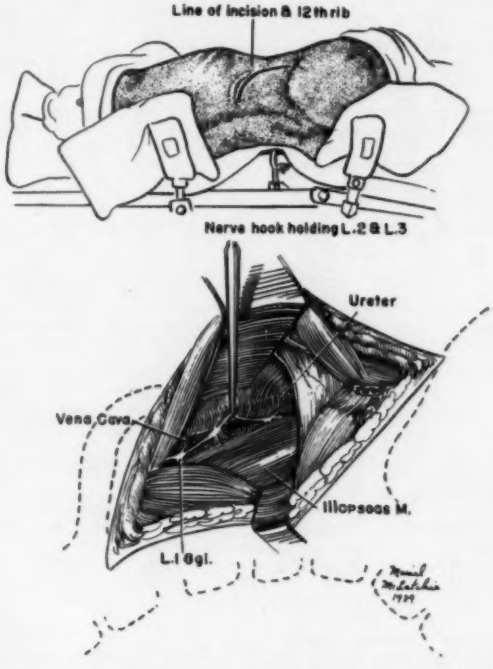

Fig. 12. Technic of operation. The lumbar sympathetic trunk is exposed extraperitoneally by an incision running forward below the twelfth rib and curving anteriorly and downward to the iliac crest. The position of the patient on the table is very important. Excellent exposure of the upper portion of the lumbar trunk is obtained. Routinely, the rami of the second and third lumbar segments are divided and a portion of the trunk containing these ganglions removed in order to prevent regeneration. If denervation of the thigh is desired, the first lumbar rami must be divided and the corresponding ganglion removed as well. For further details, see references to other articles.

Tables 7, 8 and 9 are devoted to a summary of the results of surgical treatment of thromboangiitis obliterans in terms of incidence of major amputations. An attempt has been made to show the relative value of

TABLE 5.—*Clinical Results for Upper Extremity (Group 4*)*

Diagnosis and Treatment	No. of Cases	No. of Extremities	Excellent Result	Improved	Unimproved
Rheumatoid arthritis with vascular spasm	5	7	3	2	2
Ramisectomy	..	4	..	2	2
Anterior root section	..	3	3	..	..
Causalgia with vascular spasm; anterior root section	2	2	2	..	..
Hypertension; marked vascular spasm after splanchnic resection; anterior root section	1	2	2	..	..
Thrombosis of brachial artery with scalenus syndrome	2	3	3	..	..
Ramisectomy	..	2	2	..	..
Anterior root section	..	1	1	..	..
Arteriosclerosis with gangrene and ulceration	6	10	4	5	1
Ramisectomy	..	6	2	4	..
Anterior root section	..	4	2	1	1
Thromboangiitis obliterans with ulceration and gangrene	4	4	..	4	..
Ramisectomy	..	3	..	3	..
Anterior root section	..	1	..	1	..
Totals	20	28	12 (42.9%)	13 (46.4%)	3 (10.7%)

* A miscellaneous group in which some obliterative vascular disease was present in many instances or in which the vascular spasm was secondary to some underlying condition.

TABLE 6.—*Clinical Results for Lower Extremity**
(May 26, 1936 to March 22, 1939)

Diagnosis	No. of Cases	No. of Extremities	Excellent Result	Improved	Unimproved
A. Vasospastic Disorders					
Raynaud's disease	9	18	18	..	..
Vascular spasm and old poliomyelitis	2	3	3	..	..
Vascular spasm and degenerative spinal cord lesion	1	1	..	1	..
Vascular spasm and spina bifida	1	1	..	1	..
Vascular spasm and recurrent lymphoangiitis, ulceration and epidermophytosis	1	1	1	..	..
	14	24	22	2	0
B. Obliterative Vascular Disease and Vascular Spasm					
Thromboangiitis obliterans	30	52	22	27	3
Arteriosclerosis with gangrene	4	6	2	4	0
Frostbite with gangrene	1	2	0	1	1
Gunshot wound of femoral artery	1	1	0	0	1
	36	61	24	32	5
Grand totals	50	85	46	34	5

* Sympathectomized by the extraperitoneal operation illustrated in figure 12. They are divided into two groups according to whether obliterative vascular disease was present.

different methods of treatment in similar cases. The value of sympathectomy is emphasized, and the relation of the end result to pulsation in the main vessels is brought out.[23]

TABLE 7.—*Thromboangiitis Obliterans: Incidence of Major Amputations After Various Forms of Treatment* *

	No. of Extremities	No. of Amputations	Minor Amputations	Percentage of Major Amputations
Consecutive cases before introduction of nerve block, with minor amputation when necessary..	31	23	7	74.2
Consecutive cases of nerve block and minor amputation when necessary.....	26	8	14	30.8
Consecutive cases of nerve block, and minor amputations when necessary and sympathectomy..	20	3	14	15.0

* This table is presented to show the improvement in the end results of the treatment of thromboangiitis obliterans as measured by the incidence of major amputations. The value of the addition of nerve block and sympathectomy to minor amputation (toes) and other conservative measures (cessation of smoking, careful foot hygiene, active and passive vascular exercises) is brought out.

TABLE 8.—*Thromboangiitis Obliterans: Relation Between Pulsation of the Main Vessels and Amputation* *

Diagnosis	No. of Extremities	No. of Major Amputations	Percentage of Major Amputations
(A) Popliteal pulsation present; consecutive cases of nerve block and minor amputation when necessary.....	16	4	25.0
(B) Consecutive cases of nerve block, minor amputations when necessary and sympathectomy.....	27	0	0
(A) Popliteal pulsation absent; consecutive cases of nerve block and minor amputation when necessary.....	17	8	47.1
(B) Consecutive cases of nerve block, minor amputation when necessary and sympathectomy.....	23	3	13.0

* Cases of nerve block without sympathectomy are contrasted with cases in which both procedures were used. They are subdivided according to the presence or absence of popliteal pulsation in order to compare similar cases as far as possible. The addition of sympathectomy appears to have been helpful in reducing the incidence of major amputations.

TABLE 9.—*Thromboangiitis Obliterans: Results of Treatment of Fifty Consecutive Extremities by Sympathectomy in Addition to Other Forms of Treatment* *

Patency of Main Vessels	No. of Extremities	Nerve Block Necessary	Amputation Unnecessary	Minor Amputation Necessary	Major Amputation Necessary
All patent	8	0	8	0	0
Either or both dorsalis pedis and posterior tibial obliterated (popliteal present)	19	5	16	3	0
Popliteal obliterated	21	14	8	11	2
Femoral obliterated	2	1	1	0	1
Totals.....	50	20	33	14	3 (6%)

* In all instances sympathectomy was performed, with other surgical measures as indicated. The incidence of major amputations was 6 per cent. These came in the group with the most advanced degree of main vessel obliteration. Compare with table 7 before the advent of peripheral nerve block and sympathectomy.

23. Smithwick, R. H., and White, J. C.: Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, Surg., Gynec. & Obst. **60**:1106, 1935.

SUMMARY AND CONCLUSIONS

Sympathectomy yields its most satisfactory clinical results when it is performed in such a way that the area is completely denervated by a preganglionic procedure. It is important also that the operation be performed in such a manner as to guard against regeneration.

The most brilliant results are obtained in cases of purely vasospastic disorders. However, worth while improvement may often follow if sympathectomy is performed when both obliteration and spasm of arteries are known to exist.

Various methods of testing for vasospasm are discussed. The value of studying reflex vascular and sweat gland activity is emphasized, particularly with regard to determining both the completeness and the permanence of the results of any operative procedure. The importance of clinical observation and judgment based on experience is mentioned in connection with the selection of cases for operation.

Various changes which take place after sympathectomy are considered in some detail. The difference between complete and incomplete sympathectomy is brought out. The question of "relapse" due to partial regeneration of sympathetic pathways is discussed with particular reference to reflex vascular and sweat gland activity.

The operative technic which has been found to produce the most satisfactory denervation of both upper and lower extremities is described briefly.

Clinical results in cases of both primary and secondary vasospastic disorders are tabulated. The results of various surgical measures utilized in the management of patients with thromboangiitis obliterans are discussed in terms of incidence of major amputations.

HEPARIN IN SURGICAL TREATMENT OF BLOOD VESSELS

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The valiant efforts made by many investigators to advance the treatment of diseases and injuries of blood vessels have been hampered by thrombosis and clotting in these structures. The uncontrollable factor leading to failure in many cases is not the giving way or leaking of suture lines or weakness, dilatation or stenosis of blood vessels but is occlusion of the vessels by thrombosis. The discovery of the anticoagulant heparin by Howell [1] in 1916 was therefore an epoch-making event. More recently, experiments by Murray and his co-workers [2] demonstrating that heparin would also prevent thrombosis were of importance in developing this subject. The final purification of heparin by Best and by Charles and Scott [3] made it safe to give this substance to clinical patients.

EXPERIMENTAL DATA

Heparin is a strong organic acid, probably a mucoitin trisulfuric acid. In addition to preventing clotting, it has an important effect on the platelets, preventing their clumping and thereby preventing thrombosis. Its mode of action in this respect is not understood at present. Heparin is obtained from various animal tissues, the lung giving the highest yield for purposes of mass production.

Toxicity.—The earlier preparations of heparin contained large quantities of impure material which made them too toxic for clinical administration. With further purification, however, these impurities have been eliminated, and now, with the availability of the crystalline barium salt, the toxic effects have disappeared. Within the last few months some lots of heparin appearing on the market have shown some of the

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From the Toronto General Hospital.

1. Howell, W. H.: Two New Factors in Blood Coagulation—Heparin and Proantithrombin, Am. J. Physiol. **47**:328, 1918.

2. Murray, D. W. G.; Jazues, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**:163, 1937.

3. Charles, A. F., and Scott, D. A.: The Preparation of Heparin from Beef Lung, Tr. Roy. Soc. Canada (Sect. 5) **28**:55, 1934; Studies on Heparin: I. The Preparation of Heparin, J. Biol. Chem. **102**:425, 1933; The Purification of Heparin, ibid. **102**:437, 1933.

toxic effects which were observed in the earlier preparations; however, more recently these impurities appear to have been removed, and the substance is now nontoxic.

Effect of Injection of Heparin.—Within a very short time after an adequate intravenous dose of heparin is given the clotting time rises rapidly, the level depending on the dose. If a single dose is given, the clotting time begins to fall within a short time, and from then on it descends rapidly until a normal level is reached (within an hour or two). If after the initial dose the injection is continued intravenously the clotting time can be maintained at any desired level. When administration of heparin is stopped and the clotting time returns to normal, there are no ill effects, and the blood appears to be normal in all respects.

Methods of Administration.—It was found that heparin could be administered in various ways. Local application was not particularly effective. Subcutaneous and intramuscular injections were only moderately effective. The best method, which has been used most generally in this experimental and clinical work, is continuous intravenous injection in dextrose solution or physiologic solution of sodium chloride. The injection must be made at such a rate that the clotting time is maintained at a predetermined level, usually two or three times the normal.

When operation or repair of single blood vessels is undertaken, heparin may be injected through a needle with a pump just proximal to the areas of repair. The blood stream passing over these areas will have an increased clotting time, which is not evident in the remainder of the vascular system.

Effect of Heparin in Prevention of Thrombosis.—The earlier work of Howell demonstrated the ability of heparin to prevent clotting of blood, but there was some doubt at this time whether it would prevent thrombosis. To investigate this problem, superficial veins in the extremities of animals were damaged. On mechanical and chemical irritation of segments of these vessels, occlusion took place in a high percentage. When under similar conditions heparin was given, occlusion did not take place. From several hundred experiments it appeared that heparin was effective when adequate concentrations were maintained in the blood stream.

Arterial Anastomosis.—End to end suture of arteries has been carried out successfully by many workers, and by the unprecedented technic of Carrel success has been obtained in a high percentage of cases. My associates and I carried out a fair number of anastomoses with success, and the vessels remained patent when an extremely careful technic was followed. With less care in the operation a large percentage became occluded again, by a thrombus at the suture line. When

smaller vessels, such as the brachial and femoral arteries, were sutured, practically all of them became occluded with thrombus. Of over 50 experiments in which heparin was used, the arteries remained patent in more than 80 per cent, as compared with 35 per cent for the controls. In a similar group, with improved technic in administering heparin, all the vessels remained patent. If administration of heparin was continued for seventy-two hours or more, the vessels remained patent. The intima was healed completely, without signs of stenosis or bulging. Specimens recovered many months afterward showed only a slight scar at the site of anastomosis (fig. 1).

At this stage my interest was aroused in the healing of the suture lines. Figure 2 shows the stages of repair at different intervals after operation (fig. 2).

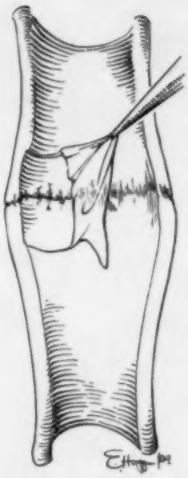

Fig. 1.—End to end anastomosis of an artery, showing healing of the suture line.

Venous Grafts.—Venous grafts have been suggested and have been tried by various workers, but I have been unable to find reports of cases in which they were used successfully, either experimentally or clinically. It was thought that, with thrombosis in 100 per cent of control venous grafts, this would be an excellent test of the effect of either regional or general heparinization. Segments of carotid arteries were excised, and a similar length of external jugular vein was removed and anastomosed at both ends to take the place of the artery. The suture material was fine silk. The operations were done quickly and without the extreme care used in Carrel's technic (fig. 3).

There was some doubt in the earlier stages whether the thin-walled vein would withstand the high arterial pressure. Under this pressure the venous grafts ballooned out in a sausage shape, and the wall when

stretched was so thin that eddies of circulating blood could be seen through it. The anastomosis in these cases was carried out with a single suture line, as it was found by repeated experiments that reenforcement with stitches or other materials was unnecessary. The whole question of success or failure depended on whether thrombosis occurred at the suture lines and not on the giving way of the wall of the vessel. It was found during the experiments that it was better to make the venous

Fig. 2.—*A*, end to end suture of an artery, showing absence of healing twenty-four hours after the operation. *B*, end to end suture of an artery, showing perfect healing forty-two days after the operation. The silk suture used in the anastomosis is shown in cross section.

graft considerably longer than the segments of artery removed, so that flexion of the animal's neck would not tear the suture lines. In all the control experiments the grafts became occluded in a short time with blood clot. When heparin was given and its administration continued for not less than seven days, the grafts remained patent. There was con-

siderable difficulty in continuing heparinization for this length of time without interruption and without complication, such as pneumonia, infection of the wounds or disconnection of the apparatus. Over 50 such grafts have been made, and many of these have been exposed surgically at intervals of three months. When the operation was completed successfully and the heparinization carried out without interruption, the grafts remained patent. Several of these grafts have been opened at the time of operation and pieces removed from the wall to study the changes in the venous wall under the change in environment. It was interesting to find that the wall of the venous graft was considerably thicker and more opaque than when it was inserted. If the original venous graft was much larger than the adjacent segments of the artery, the size of the lumen changed during the succeeding few

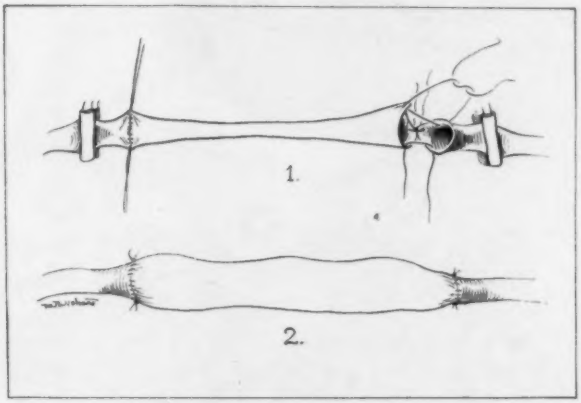

Fig. 3.—Technic of applying a venous graft.

months, diminishing considerably, so that it more nearly approximated the size of the artery. After a few months the wall of the graft was of about the same thickness and had about the same translucence as the adjacent wall of the artery. The surface had the appearance of a thick, fibrous structure with multiple small bleeding points, such as are seen in an ordinary scar. It was adherent to all the structures surrounding it but could be separated with ease. The wall was tough, and on no occasion was it torn during the dissection. There was no evidence of degeneration of the wall in the form of calcareous plaques or bulging. The vessels conducted the blood stream and pulsated normally, as did the adjacent arteries. The wall was elastic and compressible like the wall of an artery. Figure 4 shows a specimen removed after forty-two days. The changes described, such as the increased thickness of the wall, the healing of the suture line and the diminution of the lumen, are apparent. The intima appears normal, with no evidence of degeneration.

Embolectomy.—Since the first successful embolectomy, performed in 1911 by Key,[4] efforts have been made to apply this method of treatment to peripheral arterial embolisms. Failure in many cases has resulted from thrombosis at the site of operation or at the site at which the embolus was lodged. The recent application of passive vascular exercises by Reid and Herrmann has saved a great many extremities from gangrene, but it is felt that in many cases if the embolus had been removed early and the circulation restored, the ideal would have been attained. Experiments on the blood vessels of dogs were carried out to investigate the possibilities of embolectomy combined with the use of heparin.

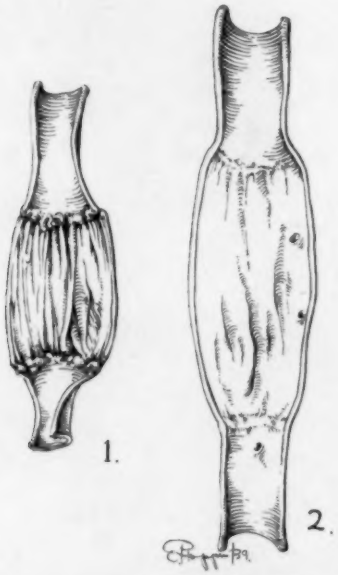

Fig. 4.—Venous grafts removed (*1*) eight hours and (*2*) forty-two days after the operation. Note the difference in the texture and in the lumens of the grafts.

Peripheral vessels in dogs were plugged with foreign bodies and blood clot and were closed. The plugs were removed after periods varying up to three days. Figure 5 shows a section of a vessel at six hours compared with a section of a vessel at forty-eight hours after such an embolus had been placed in the lumen. In the earlier hours the plug is quite free from the intima and can be removed without difficulty, whereas later there are a great deal of reaction in the intima, invasion by leukocytes and adherence of the embolus to the wall. At this stage the plug can be removed only by scraping it off the surface. After

4. Key, E.: Ueber Embolectomie als Behandlungsmethode bei embolischen Zirculationsstörungen der Extremitäten, Acta chir. Scandinav. **54**:341, 1921.

removal of such an embolus after forty-eight hours, the vessel became occluded again within a few hours. If, however, the animal was successfully heparinized for several days, the vessel remained patent and the intima healed over. Specimens removed a month later showed the artery to be clear of thrombus and to be carrying on the circulation

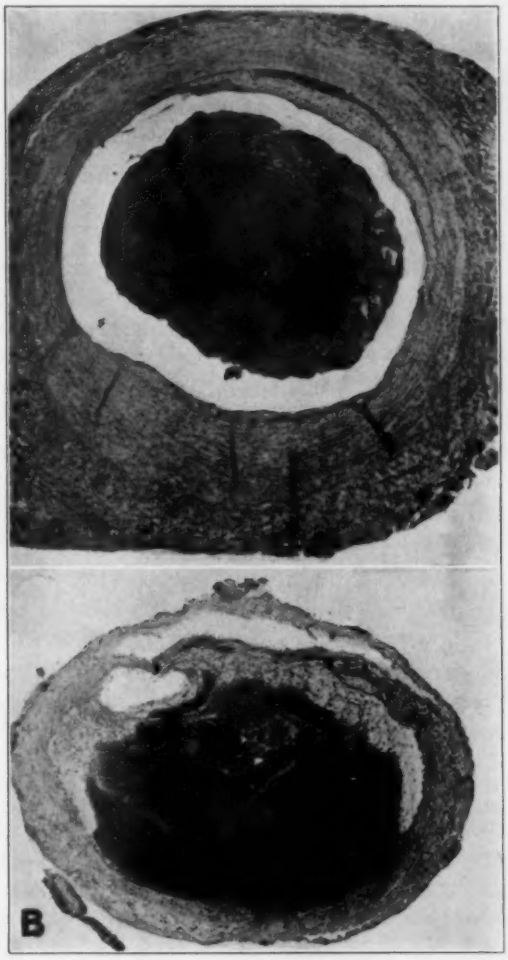

Fig. 5.—*A*, cross section of an arterial embolus of six hours' duration. The embolus is free from the wall of the vessel. *B*, inflammatory reaction produced in the wall of the vessel by an embolus which has been in place for forty-eight hours.

normally. This gave encouraging evidence that embolectomy in human patients might be carried out more successfully than formerly if heparin were used.

Effect of Heparin on Portal Thrombosis.—The knowledge that splenectomy in human beings has frequently been complicated by portal and systemic thrombosis encouraged my associates and me to perform some experiments to see whether heparin would be as effective in the portal system as in the systemic. In a group of animals the spleen was removed and the splenic vein injured. In all the controls the splenic vein became thrombosed; when, however, heparin was given successfully for seven days or more, the splenic veins remained patent in 90 per cent of cases. This also was encouraging evidence that heparin might be used to advantage in operations involving the vessels of the portal system.

Transplantation of Organs.—Many successful experimental transplantations of organs have been carried out. In our hands, however, there was a high percentage of failures. With such operations as transplantation of the kidney in animals, the circulation was maintained in relatively few instances. If, however, heparin was given after the operation and its administration continued for several days, the vessels remained patent and the end results were much more satisfactory.

Further evidence of the effectiveness of heparin in preventing thrombosis was provided by repeating Shionoya's [5] experiments of placing a transparent tube as a shunt between the arterial and the venous system. Under ordinary conditions this tube filled rapidly with thrombus. When, however, heparin was given in sufficient concentration, the tube remained clear.

Coronary Occlusion.—By irritating the coronary arteries of animals with sclerosing solutions, Best and Solandt [6] showed that thrombosis occurred in a high percentage of cases. When, however, heparin was given, this could be prevented. They found also that the mural thrombus forming with relation to the infarcted area in the chambers of the heart did not occur when heparin was used.

CLINICAL DATA

Experimental work on heparin was undertaken in the hope that this substance might eventually be used clinically for diseases in which thrombosis in blood vessels presents an unsolved problem. Thrombosis occurs spontaneously in a large group of cases of diseases of the venous and arterial systems. Such diseases are followed not infrequently by such complications as embolism, resulting in devitalization of tissues and in some cases progressing to gangrene. Pulmonary embolism is

5. Shionoya, A. T.: Studies in Experimental Extracorporeal Thrombosis: Effects of Certain Anticoagulants (Heparin Hirudin) on Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, J. Exper. Med. **46**: 19, 1927.

6. Solandt, D. Y., and Best, C. H.: Heparin and Coronary Thrombosis in Experimental Animals, Lancet **2**:130, 1938.

one of the dreaded complications, resulting in some cases in sudden death and in others in prolonged illness with persistent disability. In another group of cases, thrombosis may destroy the results of surgical treatment of aneurysms, removal of important vessels for invasion by tumor or ligation of important vessels, such as the common and the internal carotid artery.

With experimental evidence to prove that heparin would prevent thrombosis, my associates and I began giving it to patients. Former attempts by Mason,[7] McClure and others to use heparin for blood transfusions showed that it was too toxic to be of practical use. However, with the purified form of heparin available, we determined to make an attempt to use it clinically. In the first case, regional heparinization through the brachial artery was carried out successfully. After this, other patients were given heparin intravenously, but toxic effects were observed with the 250 unit material. With further purification by Charles and Scott, the crystalline barium salt was obtained, and this was found to be nontoxic. The dose was increased until, on several occasions, a clotting time of one and one-half hours was reached without ill effects. To several patients heparin has been administered at intervals of several months without signs of anaphylaxis.

Arterial Suture.—The usual surgical practice when a large vessel is bleeding is to apply a ligature. In most circumstances this is all that is necessary, and recovery is prompt. There are cases, however, in which it is more desirable to restore the circulation if possible. With the use of heparin, operations for repair of holes in vessels or for end to end anastomosis may be quite successful, as is shown by the following group of cases. The first case will be reported in detail; the others, in summary.

REPORT OF CASES

A patient's arm in the region of the elbow was severely crushed in a motor accident. Within a few hours the hand was cold, dark blue, insensitive (with no pulsations at the wrist) and greatly swollen in the antecubital fossa. It was obvious that the lower end of the brachial artery had been severely injured. At operation it was discovered that the brachial artery about 1½ inches (3.2 cm.) above its bifurcation was torn across completely and the ends separated for a distance of 1½ inches. Both ends were plugged with clot. This clot was cleared out, and the ragged ends were trimmed off until a sound segment of wall was reached. With three stay sutures in place, an end to end anastomosis was carried out with a continuous suture of silk. Heparin was injected into the vessel at this time, and a continuous intravenous injection of heparin was carried on for five days more. The vessel functioned normally and has continued to do so for one and one-half years. The patient is back at his work as a garage mechanic, and the arm is normal in all respects. This was the type of case in which ordinarily, if operation were decided on, the ends of the vessel would have been tied. From

7. Mason, E. C.: Note on the Use of Heparin in Blood Transfusion, J. Lab. & Clin. Med. **10**:203, 1924.

the amount of injury and crushing of the brachialis anticus muscle and other structures, including the collateral vessels in front of the elbow, it is more than probable that gangrene would have supervened in the hand if the vessel had not been repaired.

The extensive collateral circulation in cases of arteriovenous aneurysm allows radical ligation of the main vessels involved and excision of the aneurysm if desired. With the use of heparin, however, reconstruction of vessels can be carried out successfully if it seems to have any advantage over other methods of treatment. We have operated in 3 such cases, and in all of these the vessels were reconstructed with a satisfactory result.

In 1 case a bullet passing through Scarpa's triangle had produced two arteriovenous aneurysms between the superficial and deep femoral arteries and their corresponding veins. The aneurysms were removed and the vessels reconstructed, and heparin was administered intravenously. The circulation in the extremity has remained normal since that time. Two arteriovenous aneurysms (one in the axilla and the other in the groin) have been operated on and the vessels repaired successfully, with a return to normal of the circulation of the extremities.

In another case, during an operation for partial thyroidectomy by an excellent surgeon the common carotid artery on the right side was divided across just below its bifurcation. In this case also the accepted treatment would have been to tie both ends of the carotid artery. Although this would have been successful in most such cases, there is the danger that in about 25 per cent the patient would have cerebral symptoms, with hemiplegia in some instances and death in others. Under these circumstances it was highly desirable to repair the vessel if possible to eliminate these dangers.

After the vessel had been trimmed of its damaged portions, there was considerable difficulty in bringing the ends into apposition. However, by flexion, lateral bending and rotation of the neck this was accomplished. With three stay sutures in place, the anastomosis was carried out with a continuous line of silk suture. Heparin was injected at the site of anastomosis, and injection was continued intravenously for several days. Immediately after removal of the arterial clips, the circulation was restored. The patient's head and neck were supported in a plaster cast to prevent stretching at the site of the anastomosis. There was no evidence of any peripheral or central impairment from the accident or from the operation for repair of the vessel and the patient recovered.

Venous Grafts.—When accidents or pathologic lesions destroy segments of major arterial trunks, the usual procedure is to ligate the vessels involved. The disastrous results sometimes following such procedures have led surgeons to attempt end to end sutures of the vessels

involved, and cases have been recorded in which successful results were obtained. In a large percentage, however, the operation has failed because of thrombosis occurring at the involved area. In important vessels, such as the internal carotid artery, the aorta and the major trunks to the extremities, disaster sometimes follows obliteration of the vascular trunks. The results of experiments with suture of arteries and the use of venous grafts were so satisfactory that it was hoped that these principles might be applied to human beings. After a successful experience in 1 case, my associates and I propose, in suitable cases, to repair vessels with venous grafts when they cannot be sutured end to end.

The clinical case in which our experience of venous grafting was obtained was one of popliteal aneurysm. The swelling was enlarging rapidly and gave the impression that it would burst. The leg was paralyzed; there was a great deal of pain, and the circulation below the knee was impaired. The pulses at the ankle were weak compared with those on the opposite side.

On removal of the aneurysmal sac at operation a gap of 3¼ inches (8.2 cm.) was left between the ends of the popliteal artery. The artery was degenerated and dilated, and the wall was thickened. These changes were much more marked in the proximal than in the distal segment. It was appreciated that the collateral circulation would probably be sufficient to prevent gangrene of the foot, but the high incidence of gangrene following ligation of the popliteal artery was also considered. As this seemed a suitable case in which to attempt a venous graft, the external jugular vein on the right side was removed. This specimen was considerably smaller than the artery, and it was appreciated that it was not an especially suitable graft in this particular case. Anastomosis was carried out between the venous graft and the segments of the artery. There was a great disparity in size between the artery and the graft, and it was necessary to stretch the graft greatly to complete the anastomosis. It was feared that the stretching necessary to make the vein reach the size of the artery would damage its wall. Moreover, the aneurysm had excavated the tissues on the popliteal surface of the femur, so that the graft on this surface was stretching across an open space which ultimately would become filled with blood clot. On its superficial aspect, viable tissues were closed to give it support. Heparin was injected into the segments of the artery and the graft, and the clips on the artery were removed. Immediately the circulation returned to the foot, and there was distinct and forcible pulsation in the vessels at the ankle. The graft when fully distended was less than half the size of the adjacent segments of the artery. However, the circulation was carried on quite satisfactorily through it. The patient was given heparin intravenously to keep the clotting time at a level of about fifteen minutes for two weeks (fig. 6).

The circulation remained normal in the foot for two and a half weeks after operation. At this time the patient rather suddenly noticed a recurrence of pain in the popliteal space. With a stethoscope a bruit could be heard distinctly, and the pulsation of the vessels in the foot was less distinct than formerly. It was obvious that another aneursym had occurred. The popliteal space was again explored. There was a large false aneurysm, the walls of which were removed. The venous graft and segments of the artery were exposed. These were normal in every respect, and the circulation was being carried on. The wall of the venous

graft was thicker than at the original operation, and it showed the changes which our experience with animals had led us to expect. The only defect was at an area about ¼ inch (0.6 cm.) distal to the proximal suture line. Here the wall of the venous graft on its anterior surface had bulged, forming a small aneurysm about ⅝ inch (1.8 cm.) in diameter. At one point this small aneurysm had given way, and through this opening it communicated with the false aneurysm. When this opening was occluded and the circulation allowed to return, there was normal pulsation in the vessels of the foot, and the pulse could be demonstrated in the venous graft and in both segments of the artery. With clips on the segments of the artery, a probe could be passed through the opening in the aneurysm and through both suture lines; there was no obstruction or stenosis. (From the

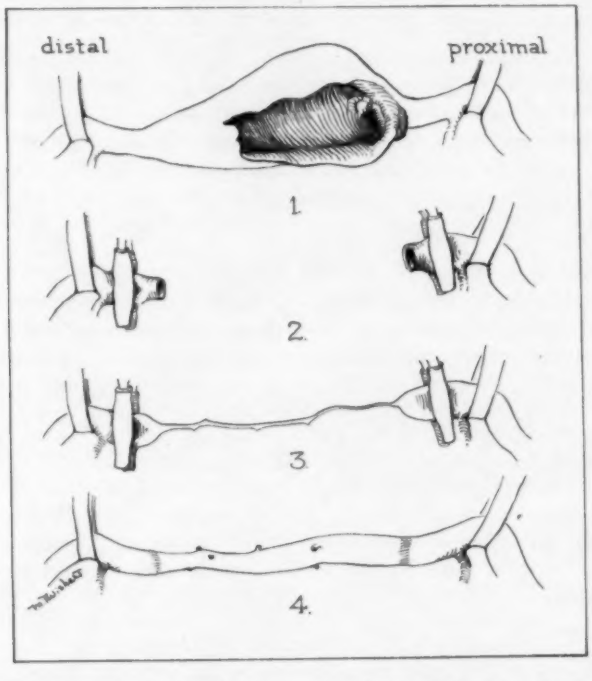

Fig. 6.—Stages of resection of an aneurysm and application of a venous graft in the popliteal artery in a clinical case.

evidence found at operation it was obvious that the venous graft had given way at a point at which it had been overstretched. On another occasion a larger vein, matching the size of the artery more accurately, will be used.)

We were in doubt whether the graft should be excised and the arteries ligated. It was decided, however, to repair the aneurysm. Flaps were cut in such a fashion that the lumen of the vessel was maintained and the aneurysm repaired. When circulation was restored after this, there was excellent pulsation in the graft and in the distal segment of the artery, although this was less forcible than before. The

patient was again heparinized. The circulation in the foot remained normal, and at the time of writing, fourteen months after the operation, the patient is able to do light work.

This was a most instructive case, as it demonstrated the possibility of using a venous graft to bridge a gap in an artery in a human being. It showed that the graft survives when the patient is treated with heparin, that its wall becomes thickened and that stenosis does not occur at the suture lines. The failure of a small area of the graft was probably due to the overstretching which was necessary to make the vein fit the artery.

Even if such a graft functioned for only a few days it might overcome the dangers resulting from acute failure of circulation, under many conditions. There is evidence, however, that the graft may survive and function indefinitely.

Mesenteric Thrombosis.—Whatever the underlying cause of mesenteric thrombosis may be, the most important pathologic change associated with the disease is thrombosis of mesenteric vessels. As this continues to spread even after resection, the mortality rate for this disease is high. It appeared, therefore, on the experimental evidence, that heparin might be of value in preventing the spread of thrombosis in this disease. In 6 cases in which there was gangrene requiring resection of from 18 inches (45 cm.) to 7 feet (2 meters) of bowel, heparin was given immediately after the operation. According to the experience of the surgeons operating in these cases, none of the patients would have survived. It is interesting, therefore, to report that the first 4 are still alive and well more than a year after their operations. In the case of the fifth the diagnosis was made late in the course of the disease. The patient died twenty-four hours after resection of the bowel. At postmortem examination there was no extension of gangrene, and the peritoneal cavity was normal; the patient had died of bilateral bronchopneumonia. In the sixth case, 7 feet (2 meters) of the terminal portion of the ileum, the cecum and the ascending colon was resected because of extensive gangrene with grayish, sloughing, foul-smelling bowel with peritonitis already in a fairly advanced stage. The patient lived nine days; at postmortem examination there was no extension of the gangrene in the bowel, and, although the patient died of peritonitis, it was the pathologist's opinion that the condition had persisted from the serious peritoneal infection which was present at the first operation.

Considering the high mortality from this disease, it probably is a significant fact that the first 4 patients of this series recovered without complications and are still alive and well. The next 2 died of late complications of the disease and not of extension of thrombosis in the mesenteric vessels. This evidence would indicate that when there is sufficient gangrene of the bowel to require surgical resection in cases of mesenteric thrombosis it would be a great advantage to use heparin

immediately after the operation. My associates and I continue injection of heparin for periods varying from ten days to two weeks, keeping the clotting time of the blood between fifteen and twenty minutes.

Splenectomy.—With experimental and clinical evidence that heparin is effective in the portal system, it was thought that it might be used to prevent portal and systemic thrombosis following splenectomy. In certain diseases (such as familial jaundice) for which splenectomy is done, the mortality rate is high because of portal thrombosis. We have given heparin postoperatively to a group of 8 splenectomized patients. While this group is too small from which to draw conclusions, it was interesting to note that in none did thrombosis develop in any form. From our knowledge of the effect of heparin in preventing thrombosis, it would seem advisable to give heparin postoperatively to splenectomized patients in whom thrombosis is likely to occur.

Blood Transfusions.—A large number of blood transfusions have been done with the use of heparin as an anticoagulant. It has been given to the donor so that the blood may be drawn without clotting. In some cases the heparin has been added to the drawn blood. If the blood is to be given immediately to the recipient, from 1 to 1½ units of heparin per cubic centimeter of drawn blood is sufficient. The small amount necessary is inexpensive compared with some of the other anticoagulants in use.

Embolectomy.—Clinical experience has shown that unless an embolus is removed from a peripheral artery within ten or twelve hours the prognosis is not good. The results of this operation are increasingly bad with further lapse of time. Moreover, even in the earlier phases failures are due frequently to a thrombus obliterating the vessel, either at the operative site or where the embolus is lodged. The weakened condition of the patient with chronic heart disease, high venous pressure or low blood pressure contributes to the formation of a thrombus. It was thought, therefore, that heparin might be of great value in this operation.

Twelve arterial embolectomies have been done and heparin used postoperatively. In all cases this procedure was successful if the lumen was cleared completely and the circulation restored. Heparin was injected into the vessel at the site of operation and the injection was continued intravenously for from three to fourteen days. In all 12 cases the vessels remained patent, and the circulation has been maintained in the extremities.

Two of the patients died at different intervals after the operation. In 1 case autopsy enabled us to prove that restoration of the circulation had taken place. This patient had been operated on twenty-five hours after the first appearance of symptoms of embolism involving both the common iliac and the femoral arteries. The emboli were removed with moderate difficulty, as they tended to stick to the intima of the vessels.

Heparin was injected locally, and when the clips were removed the circulation returned quickly to both feet. The clotting time of the blood was kept at twenty minutes for two weeks; then heparin was discontinued. The circulation remained normal in the feet, and the patient made an excellent recovery. The patient died later of other lesions. The aorta and the vessels going to the legs were recovered. These were all perfectly clear, with no sign of thrombosis or clots either at the operative site or in the areas where the emboli had lodged. The incision through which the emboli were removed was perfectly healed. A photomicrograph of the tissue through which the incision had been made showed the intima to be healed perfectly, with no sign of thrombosis or clotting. In the other case, in which the patient died twenty-four hours

Fig. 7.—Common, superficial and deep femoral arteries removed twenty-four hours after embolectomy in a clinical case. The suture line is firm and smooth, with no sign of thrombosis or clot.

after the operation, the vessels were quite clear, with no sign of thrombosis or blood clots. The suture line was intact (fig. 7).

Although in most cases of peripheral embolism blockage is incomplete and in others there is sufficient collateral circulation, gangrene of the extremities often develops, necessitating amputation. Many patients respond to treatment with the pavaex machine, but in my experience this device will not prevent gangrene in all cases. It is suggested, therefore, that if operation is done within the first twenty-four hours and combined with the use of heparin better results may be expected.

Phlebitis.—Although phlebitis is considered by some to be a "medical disease," its incidence as a postoperative complication only too often brings it to the surgeon's notice. The striking improvement of the

symptoms of this disease under treatment with heparin probably warrants a short discussion of the subject. Unquestionably there is a considerable difference in cases of thrombophlebitis. Thrombi occurring in varicose veins probably have a different origin from those observed in cases of phlegmasia alba dolens. It was with extreme interest, therefore, that my associates and I watched the course of patients with this disease. It was observed that the earlier heparin was administered after the beginning of an attack of phlebitis, the more effective was the treatment. Although there is great variation in the course in different cases of thrombophlebitis, we were impressed by the fact that the recovery was more rapid and more complete in patients treated with heparin than in a group of controls. Within a few hours, the symptoms were much improved, pain was diminishing or had disappeared and the temperature had begun to fall and within a few days had returned to normal. The edema began to recede within one or two days and frequently disappeared completely within a week or ten days. Although it is too early to judge the end results, there has been less persisting edema than in the control group. Pulmonary embolism, the common complication occurring in 15 per cent of 300 cases, did not occur in 81 cases in which heparin was used. In 5 cases of migrating thrombophlebitis the symptoms disappeared more slowly than in cases of the more acute forms of the disease. In 3 of these cases there were recurrences of the disease within a few months.

It is uncertain why heparin should produce these effects on thrombophlebitis. The only effect that heparin could have is to prevent extension of thrombosis. It is possible, therefore, that the healing of the lesion already present is allowed to take place and that with prevention of extension of the process the active inflammation recedes and the symptoms disappear with it.

The treatment in these cases was carried out as in the others by a continuous intravenous injection, the clotting time of the blood being kept between fifteen and twenty minutes. After the first three or four days, when the acute symptoms had disappeared, the patient was encouraged to exercise actively in bed, and within an average of one week of the beginning of treatment the patient was encouraged to sit out of bed and do active leg exercises with weight bearing. The injection was continued during this period. If no untoward signs or symptoms developed by the second or third day he was out of bed, the injection was discontinued and the patient was discharged from the hospital. Most of the patients in this group of 81 cases were discharged within six to fourteen days of the beginning of treatment for acute thrombophlebitis. Except in the cases of migrating thrombophlebitis, there has not been a recurrence of the disease in two and one-half years.

Considering the great variation in different cases of thrombophlebitis, it might be expected that many of our patients would have recovered in a

short time without heparin treatment. However, we were greatly impressed by the seriousness of the disease in many of the cases, and it was amazing to see the patients recovering and out of bed in such short periods. Whether heparin had a specific effect is difficult to determine, but these patients have returned to normal activity in a considerably shorter time than the average for a (larger) group of control cases.

Thrombophlebitis and Pulmonary Embolism.—Encouraged by the spectacular results in patients with thrombophlebitis, we decided to try heparin for a group of patients with pulmonary embolism. It was realized that when pulmonary embolism develops large areas of the peripheral venous system may still contain thrombi, which may be discharged to repeat the accident at any time. As heparin has no effect in dissolving the clot, it cannot affect the thrombi in any way. Because other forms of treatment are so ineffective and Trendelenburg's operation is such a serious one, with relatively few recoveries to date, it was considered worth while to give heparin a trial. Up to the present time, 29 patients with massive pulmonary embolism have been treated with heparin. These patients all presented the usual picture of the disease, with sudden onset, marked collapse and rapid pulse. Several had multiple embolisms with infarcts which were demonstrated on clinical and roentgen examination. Heparin therapy was instituted at intervals of a few hours to several days after the attack. The results were surprisingly good. Of the 29 patients, none have died of embolism, although death seemed imminent for some. The dyspnea and other signs of the disease improved rapidly, and within twenty-four hours all the patients stated that they were improved. From that time on the symptoms rapidly disappeared. With one possible but unproved exception none of the patients had further emboli. With this disease, as with thrombophlebitis, it is impossible to predict the outcome, as it is well known that 80 per cent of patients recover. In this group, however, the involvement in many of the cases was serious, and, judging from our experience with the disease, was of the type for which the prognosis is extremely bad. It is possible that the psychic effect of some active form of treatment was important, but this factor is difficult to evaluate.

The treatment carried out in this group was similar to that in cases of uncomplicated thrombophlebitis. The patients were encouraged to exercise in bed after the third day and were allowed out of bed at periods varying between six days and two weeks.

Two other patients who were treated with heparin died, and postmortem examinations were made. The first died of general peritonitis following a partial gastrectomy, and thrombophlebitis and pulmonary embolism occurred as postoperative complications. At autopsy the infarcts of the lungs were seen to have been resolving, and there was

no recently formed clot or thrombus either in the pulmonary vessels or in the peripheral venous system. An area in the left common, external iliac and femoral veins, the region of which was obviously the site from which the embolus had come, showed some remaining thrombus, but this was firmly attached to the wall of the vein. In the second case the patient recovered after treatment with heparin and was well for four months. After this obstruction of the small bowel developed as a result of postoperative adhesions. It was discovered also that he had an actively bleeding duodenal ulcer. As this was a positive contraindication to treatment with heparin, the substance was not administered on this occasion. At autopsy in this case it was demonstrated that the patient had died of obstruction of the small bowel. There were scars of the previous embolisms which had healed on treatment with heparin. Recent pulmonary emboli had occurred during the last illness, when it was considered unwise to give him treatment with heparin because of his bleeding ulcer.

While our experience with heparin in cases of pulmonary embolism is limited to this relatively small group of cases, the effect has been so striking that we are encouraged to continue its use in future cases.

Postoperative Heparinization.—As pulmonary embolism is one of the commoner postoperative complications, it was decided to treat a group of patients with heparin in an attempt to prevent this. Four hundred and forty patients have been given heparin, the clotting time being increased to between fifteen and twenty minutes. None of these had thrombosis at the site of injection even though the steel needle was left in for periods varying between a week and two weeks. No thrombosis or embolism occurred in any patient who was free from it at the beginning of treatment, and in those who had thrombosis there was no extension of the process. Obviously this is too small a group of cases from which to draw conclusions, but it is significant that cases of many of the conditions in which thrombosis and pulmonary embolism tend to develop were included in this group.

SUMMARY

Heparin was discovered by Howell,[1] who showed it to be an anticoagulant. Further purification was carried out by Best and by Charles and Scott. Experiments by Murray demonstrated that it would prevent thrombosis.

The purified form of heparin has been shown to be nontoxic to animals. In many operations on veins and arteries it has been shown to prevent thrombosis and clotting until healing has taken place. Venous grafts in arteries have been kept patent by its use and have functioned satisfactorily for one and one-half years.

In 440 patients in the hospital treated with heparin, thrombosis and embolism did not occur. Patients with thrombophlebitis were thought to be improved by the treatment. Striking improvement was observed in a group of patients with pulmonary embolism; with 1 possible but unproved exception, none of these patients had further embolisms, and none died of pulmonary embolism. Embolectomies were successful in 12 cases when heparin was used. In 1 case a venous graft was placed in an artery; this remained patent and functioned satisfactorily. It is suggested that heparin is a most important agent for prevention of thrombosis when operation for repair of blood vessels is undertaken. Heparin might also be used to advantage for diseases in which thrombosis and clotting in the blood vessels occur.

Prof. C. H. Best collaborated with me in this work. Mr. L. B. Jaques, Dr T. S. Perret, Dr. R. Wilkinson and Dr. R. MacKenzie furnished assistance. Financial help was given by grants to these assistants by the Banting Research Foundation. The heparin used in the earlier stages of the work was donated by the Connaught Laboratories. Mr. J. S. McLean provided financially for the supply of heparin used in these experiments during the past year.

INFLUENCE OF TEMPERATURE ON THE DEVELOPMENT OF GANGRENE IN PERIPHERAL VASCULAR DISEASE

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The fact that heat is brought to the extremities by the flow of blood is generally recognized. The temperature of the part has come to be accepted as indicative of the state of circulation to the tissues. When the hands or feet are cold, it is natural to believe that the blood supply is reduced. Similarly, warmth of the parts indicates adequate blood flow.

It has long been established that the circulation to the extremities is increased by the application of heat and decreased when cold is applied. Quantitative studies [1] have demonstrated the relationship between elevated temperature and increased flow of blood. Since warmth of the extremities is closely related to the circulation and since it is recognized that the blood flow may be increased by the application of heat it is natural to attempt to correct the cold due to inadequate circulation by applying heat.

Patients with impaired circulation often complain of the coldness of their extremities. The pain which is associated with the vascular insufficiency is frequently relieved by keeping the parts warm and is increased when they are cold. Under such circumstances it is probable that the vasoconstriction brought about by the low temperature reduces the circulation. Warmth, which allows the vessels to relax, is followed by an increase in the flow of blood sufficient to supply the needs of the tissues.

From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania.

1. (*a*) Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, Heart **1**:87, 1909. (*b*) Stewart, G. N.: Studies on the Circulation in Man: I. The Measurement of the Blood-Flow in the Hands, ibid. **3**:33, 1911. (*c*) Rein, H.: Die Thermo-Stromuhr, Ztschr. f. Biol. **87**:394, 1928. (*d*) Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**:384, 1935. (*e*) Kunkel, P., and Stead, E. A., Jr.: Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis, and in Thromboangiitis Obliterans, J. Clin. Investigation **17**:715, 1938.

These needs, however, are dependent on the metabolic rate. It is well known from experiments on cold-blooded animals [2] that the metabolism is increased by elevating the temperature. It is probable that a similar relationship between metabolism and temperature exists in the tissues of warm-blooded animals. Extremities which are cold, therefore, probably have a low metabolism. Although the vasoconstriction which results from the cold may be relieved by the application of warmth, the tissue metabolism will be increased at the same time. In patients with normal blood vessels the more rapid circulation produced by heat will be able to care for the increased metabolic needs. When

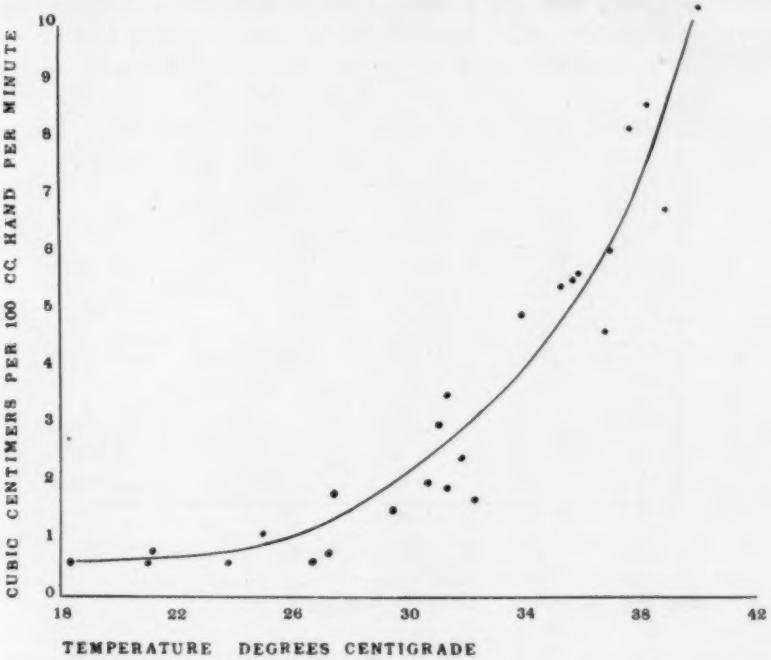

Fig. 1.—Effect of increasing the temperature of a bath, in which the hand was immersed, on the volume flow of blood through the hand. Twenty-five determinations of blood flow were made on the same patient on five successive days.

there is organic occlusion of the blood vessels so that the capacity for dilatation is limited, the circulation may not be able to develop to the extent required by the elevation of tissue metabolism. Under such circumstances the discrepancy between the needs and the blood supply of the tissues may actually be increased by the application of heat. From this standpoint the absolute blood flow is not the criterion of an

2. Krogh, A.: The Respiratory Exchange of Animals and Man, London, Longmans, Green & Co., 1916.

adequate circulation. It is the blood flow in relation to the metabolic needs of the tissues which is of significance. A diminished blood supply which is quite adequate for tissues with a low metabolism may be inadequate if the local metabolism is elevated.

Gangrene has been defined as "the dying of tissue due to interference with local nutrition." It is readily understandable that gangrene should result from complete occlusion of the blood supply. Examples of this condition are to be found in peripheral embolism or in major arterial thrombosis associated with Buerger's disease or arteriosclerotic gangrene. The blood supply may also be obstructed by extreme vasoconstriction as in Raynaud's disease. When the occlusion of the arterial supply is partial, the possibility of increase in the blood flow is limited. The

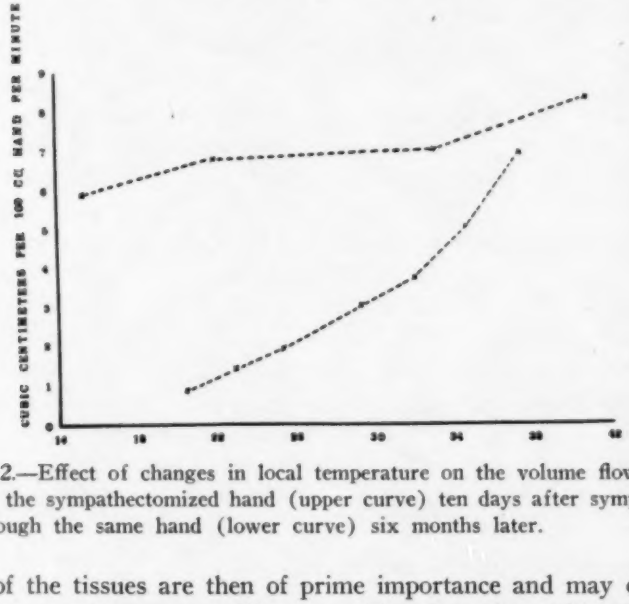

Fig. 2.—Effect of changes in local temperature on the volume flow of blood through the sympathectomized hand (upper curve) ten days after sympathectomy and through the same hand (lower curve) six months later.

needs of the tissues are then of prime importance and may determine whether or not gangrene will occur. Gangrene, from this standpoint, will occur as the result of a discrepancy between the local demands of the tissues and the supply of blood available to meet these nutritional needs. In a study of the effect of temperature on the production of gangrene it is therefore necessary not only to determine what factors influence the rate of blood flow but also to ascertain the effect which these factors exert on the local metabolism.

The quantitative relationship between blood flow and temperature not only in the normal but also in the sympathectomized hand was investigated in a study previously reported.[1d] The circulation through the hand was measured by the plethysmographic technic of Hewlett and Van Zwaluwenburg [1a] with the hand immersed in water at different

temperatures. It was found that as the temperature of the bath in which the hand was immersed was gradually increased there occurred a rise in the rate of blood flow, as shown in figure 1. Immediately after sympathectomy the circulation was stabilized, but six months later the flow was found to vary directly with the temperature. The relationship between blood flow and temperature in the sympathectomized hand is illustrated in figure 2. This observation has been repeatedly confirmed. The absence of regeneration of vasomotor fibers was checked by appropriate tests.

It has long been recognized, since the work of Roy and Brown,[3] that the tissues exert an influence on their blood supply in such a way as to increase the circulation in accordance with the metabolic needs. The increase in blood flow through working muscles was recognized by

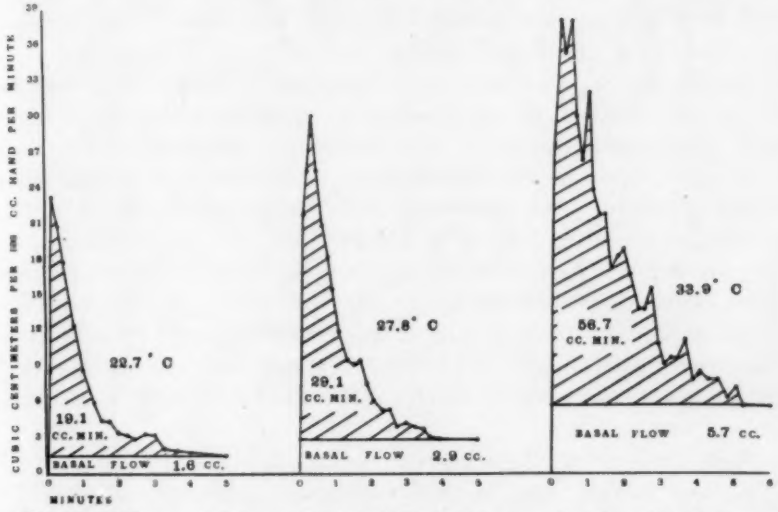

Fig. 3.—Effect of changes in local temperature on the "reactive hyperemia" which resulted after release of a tourniquet which had occluded the circulation to a sympathectomized hand for ten minutes at each of three temperatures. The excess of blood flow above the basal flow was measured with a planimeter.

Chauveau and Kaufmann[4] in 1887. If the circulation is temporarily occluded, a marked increase follows release of the tourniquet. This reaction was first described by Cohnheim[5] in 1872 and was studied

3. Roy, C. S., and Brown, J. G.: The Blood-Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879-1880.

4. Chauveau, A., and Kaufmann, M.: Expériences pour la détermination du coefficient de l'activité nutritive at respiratoire des muscles en repos et en travail, Compt. rend. Acad. d. sc. **104**:1126, 1887.

5. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, A. Hirschwald, 1872.

by Roy and Brown,[3] by Lewis and Grant [6] and by Montgomery, Moore and McGuinness.[7] They observed that the extent and the duration of the reactive hyperemia, i. e., the increase in blood flow after release of the occlusion, was dependent on the duration of the circulatory occlusion and on the temperature at which the part was maintained. Lewis and Grant [6] referred to this phenomenon as a "repayment of a blood flow debt." We studied the quantitative aspects of this reaction in the sympathectomized hand with the temperature stabilized at different levels. It was found in 17 experiments on 5 persons that whether the length of the occlusion was varied from two to twelve minutes, or whether the rate of the blood flow was altered by changing the local temperature, the equivalent of the debt was repaid. Figure 3 illustrates the response in a subject which resulted after occlusion of the circulation for ten minutes at each of three temperatures. The excess blood flow over the basal level was measured, and the total "repayment" was found to approximate the established "debt."

Further studies showed that the observed quantitative relationship held only for short durations of occlusion and at the lower temperatures. When prolonged deprivation was tried, the repayment far exceeded the debt. Pain was produced, especially at the higher temperatures. It seemed as though, with prolonged occlusion, the physiologic nature of the reaction was altered and a pathologic condition was produced. Evidence for this belief was afforded by the appearance of petechial hemorrhages in the skin when the hand was deprived of circulation for five minutes at 40 C. (104 F.). The inflammatory reaction of tissues in an extremity which has been the site of a major arterial occlusion with vascular insufficiency for an extended period of time illustrates a comparable phenomenon.

These observations gave support to the concept originally advanced by Roy and Brown [3] that the vasodilatation was brought about "either by some stimulus acting directly on the walls of the vessels, or indirectly on these through the medium of nutritive changes of the tissue elements." Since a quantitative relationship was observed between temperature, duration of circulatory arrest and subsequent vasodilatation, it seemed likely that the circulation through the sympathectomized hand with the temperature stabilized was modified by the metabolism of the tissues.

Further evidence for the peripheral control of the circulation was sought in determinations of the blood flow through sympathectomized paws of dogs together with analyses of the arterial and venous blood

6. Lewis, T., and Grant, R.: Observations upon Reactive Hyperaemia in Man, Heart **12**:73, 1925.

7. Montgomery, M. L.; Moore, J. M., and McGuinness, J. S.: Reactive Hyperemia: Relation of Duration of Increased Blood Flow to Length of Circulatory Arrest, Am. J. Physiol. **108**:486, 1934.

for oxygen and carbon dioxide.[8] It was found that in any one experiment the circulation varied directly with the temperature, although the difference between the arterial and the venous blood in respect to oxygen and carbon dioxide contents remained constant. With increase in local temperature an increase in local metabolism was therefore demonstrated. The blood flow increased simultaneously to care for the increased needs.

These observations were made in sympathectomized areas, which were free from vasomotor control, and the question may be raised whether they are applicable to tissues which are subject to vasomotor control. The control by the tissues of the quantity of blood supplied to them would appear to be a fundamental property on which the vasomotor regulation was imposed to relate the supply to any tissue to the needs of the body as a whole. Since the increase of circulation with elevation of local temperature was observed in the normal hand, and since the phenomenon of reactive hyperemia was also found in the presence of an intact vasomotor supply, it is probable that the same fundamental relationship between temperature, metabolism and circulation holds for the normal tissues also.

Since heat produces an elevation of the metabolism of the tissues, its use to promote an increase in circulation must be viewed from the standpoint of the functional capacity of the vessels. If there is organic obstruction to the flow of blood, the increase in tissue needs occasioned by the elevation in temperature may be greater than any possible improvement in circulation. An additional source of injury is presented by the fact, pointed out by Starr,[9] that the impaired blood supply will not be able to carry off the additional heat supplied from without, so that the temperature of the tissues rises to heights which are in themselves injurious.

In his discussion on the use of heat in the local treatment of peripheral vascular disease Starr [9] made the comment "It is well known that 'baking' a foot with undiagnosed peripheral vascular disease may cause gangrene: I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized." The incidence of gangrene following application of a tourniquet in Allen's [10] experiments was greatly increased even by moderate elevation of temperature.

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8. Freeman, N. E., and Zeller, J. W.: The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog with Observations on the Oxygen Content and Capacity, Carbon-Dioxide Content, and p_H of the Arterial and Venous Blood, Am. J. Physiol. **120**:475, 1937.

9. Starr, I., Jr.: On the Use of Heat, Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Disease, Am. J. M. Sc. **187**:498, 1934.

10. Allen, F. M.: Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. **68**:1047, 1939.

The influence of temperature on pain and cyanosis was studied by Starr [9] in 11 patients. He found that the optimum temperature for relief of pain and improvement of color lay somewhere between 30 and 34 C. (86 and 93.2 F.). These observations were fully confirmed by our experience. In 8 patients with obliterative vascular disease, even though no open lesion was present at the time of observation, a temperature of 42 C. (107.6 F.), which was reached by gradually heating the bath in which the extremity was immersed, either brought on or increased the local pain and always increased the cyanosis. Certain patients could not tolerate even temperatures of 35 C. (95 F.). In 1 patient it was of particular interest to observe that the pain experienced in the finger at 40 C. (104 F.) persisted for two minutes after the hand had been removed to the room air. After reproducing the pain by a second heating, it was relieved in fifteen seconds by immersion of the hand in cold water.

Although pain in peripheral vascular disease is frequently aggravated by cold and relieved by warmth, there are some patients who will seek comfort by uncovering their feet. Their objection to the application of heat is significant. The discomfort of unregulated heat is complained of. Two patients have recently been observed in whom after occlusion of the femoral artery heat was applied directly to the leg by means of a baking cradle. In each instance extensive gangrene of the foot developed, and the anterior surface of the leg which was more exposed to the radiant heat showed the more intense reaction. Next to those whose gangrene is due to infection and the necrosis which results from the application of a strong antiseptic, the greatest number of patients with gangrene who are seen in the clinic for peripheral vascular diseases seem to have had their trouble precipitated by the injudicious application of heat.

What is the optimum temperature for an extremity which is the seat of occlusive vascular disease? It is well known that cold produces vasoconstriction both through reflex action of the sympathetic nervous system and directly through its action on the smooth muscle of the blood vessels. It is desirable, therefore, to avoid cold if possible, unless temporary refrigeration of the part is desired before amputation, as suggested by Allen.[10] On the other hand, according to the present concept, heat is harmful. Each patient probably has a specific tolerance dependent on the capacity of his vessels to supply blood to the part. Again, the metabolism of the part is conditioned by the presence of infection. The oxygen-carrying capacity of the blood is also of significance. With so many variables, it is impossible to give any definite rule as to the optimum temperature. In general, it may be said that the temperature should be maintained at the highest level which does not increase the circulatory discrepancy as shown by cyanosis and pain.

Inspection of figure 2 indicates that the curve for the increase in blood flow with rising temperature ascends sharply at temperatures higher than 30 C. (86 F.). From this point upward, there is a rapid increase. It is better to maintain the temperature of the air about the foot somewhere between 30 and 34 C. (86 and 93.2 F.). With gangrene or with gangrene impending, the temperature must be kept at a lower figure.

When wet dressings are indicated, their temperature should be carefully controlled, since heat can be more readily delivered to the tissues by hot water than by hot air. It has been our practice to apply hot wet compresses to the inflammatory area above the zone of potential gangrene but to apply moist dressings at room temperature to the distal parts.

Many devices have been suggested for the regulation of the temperature of the environment about an extremity affected with occlusive vascular disease. Starr [11] and Sevringhaus [12] devised excellent thermoregulated cradles. The only drawbacks are the expense of these cradles and the difficulty of accurate regulation. The simplest one which I have found is that suggested by Montgomery and Starr.[13] The thermostat is calibrated from 85 to 105 F. My associates and I have encountered no unfortunate reactions in the past two years using these thermoregulated cradles.

SUMMARY

Gangrene results from a discrepancy between the demands of the tissues and the supply of blood to meet these nutritional needs.

Experimental investigations of the effect of temperature on the volume flow of blood through sympathectomized extremities indicate that the circulation is conditioned by the metabolic requirements of the tissues.

The metabolism of the tissues increases directly with the temperature.

In the presence of organic occlusive vascular disease, the application of unregulated heat may precipitate gangrene, since it may increase the metabolism of the tissues more than it increases the circulation.

Use of a thermoregulated cradle of simple construction is suggested in order to maintain the environmental temperature at the desired level.

11. Starr, I., Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, Proc. Soc. Exper. Biol. & Med. **29**:166, 1931.

12. Sevringhaus, E. L.: A Constant Temperature Foot Cradle, Am. J. M. Sc. **187**:509, 1934.

13. Montgomery, H., and Starr, I.: Four Physiotherapeutic Devices for the Treatment of Peripheral Vascular Disorders, Am. J. M. Sc. **197**:485, 1939.

EFFECT OF ESTROGENS ON VASCULAR SPASM DUE TO ACTIVE ANGIITIS IN THE EXTREMITIES

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Recent advances in the management of arterial insufficiency in extremities have come largely as a result of better understanding of the pathologic physiology of the peripheral circulation and recognition of the more important factors which alter the delicate functional balance in the peripheral vascular bed. Disturbances in the peripheral circulatory balance greatly interfere with the natural ability of the vascular system to respond properly to the usual physical changes in the environment.

Active inflammation of the arteries or the veins in an extremity may provoke vasomotor instability in the entire limb and occasionally in all four extremities. In the early stages of peripheral angiitis, abnormal susceptibility to mild degrees of cold may be the only clinical evidence of inflammatory involvement of the arteries and veins; yet if the true nature of such an underlying process is not recognized or if adequate therapy is delayed too long, serious structural changes in the affected blood vessels are certain to take place. We believe that careful studies of circulatory efficiency in the extremities, made under controlled conditions of temperature and humidity,[1] will usually enable the clinician to estimate satisfactorily how much of the circulatory embarrassment is due to reflex vasoconstriction, as well as how much actually results from structural changes in the peripheral arteries.

After a major or a secondary artery of an extremity has become obliterated by inflammatory changes in its wall or by formation of a blood clot within its lumen, the chance to restore its normal function has been lost. When circulatory insufficiency in the extremity is present as the result of such structural changes in the arteries, all thera-

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1. Herrmann, L. G.: Clinic on Peripheral Vascular Diseases, Internat. Clin. **3**:171 (Sept.) 1937.

peutic efforts must be directed toward promotion of a more active flow of blood through the existing collateral arteries if any permanent increase in nourishment of the tissues of the distal parts of the extremity is to be brought about.

The vasomotor instability which occurs during the early phases of thromboangiitis obliterans is well known. Some years ago it was considered so important in the symptomatology of this pathologic entity that "sympathetic ganglionectomy" or ramisection was suggested for its relief. At present most students of this problem believe that such operations accomplish only a little more than can be accomplished by much simpler means; therefore the practice of performing a sympathectomy for this condition has been abandoned by most surgeons.

In clinical practice one may observe a great variety of bizarre vascular disturbances, most of which cannot be classified accurately in the light of present knowledge. Rational treatment, therefore, may become extremely difficult or even impossible. Careful analysis of the obscure vascular problems presented frequently brings out the fact that the clinical picture is actually the result of several different disturbances. Since the true cause of any of the major peripheral vascular diseases has never been established, it becomes doubly important to recognize the major factors which contribute to vascular insufficiency in the extremity of any given patient and to direct the intensive treatment along known physiologic lines.

Since 1932 we have been interested in determining the various factors which cause high grade peripheral vasoconstriction and particularly in determining the various ways by which such secondary vasoconstriction can be altered for therapeutic reasons.

SECONDARY VASOMOTOR INSTABILITY

Most workers in the field of peripheral vascular disturbances have been impressed by the importance of vasomotor instability in all of the serious varieties of active vascular disease of the organic type, and many different ways of overcoming the associated peripheral vasoconstriction have been used successfully in the clinical management of these disturbances.

The vasomotor instability which usually results from the more extensive types of acute phlebitis and active arteritis has been shown also by many different observers to be responsible for many of the signs and symptoms. Frequently the secondary manifestations make up that part of the clinical syndrome toward which all active treatment must be directed if the more serious complications are to be avoided.

In 1932, Albert [2] published clinical and experimental proof that a high degree of peripheral arterial spasm results from acute occlusion, due to trauma or inflammation, of the major vein of an extremity. On the basis of these studies and of observations of their own, Leriche and Kunlin [3] suggested infiltration of the regional sympathetic ganglions with 2 per cent solution of procaine hydrochloride to overcome the secondary vasoconstriction. Their reports indicate that most of their patients were relieved of their symptoms by this paralysis of the vasomotor nerves to the affected extremity. Recently Ochsner and DeBakey [4] confirmed these studies and reported on several patients with thrombophlebitis who benefited greatly from blockage of the regional sympathetic pathways by procaine hydrochloride.

The apparent sex limitation of that type of active angiitis called by Buerger thromboangiitis obliterans has interested all students of these disturbances and has seemed to support the idea that the "hormone" content of the tissues in the male and in the female is of importance.

EXPERIMENTAL BACKGROUND

In 1935, one of us (McGrath) [5] published the results of his work, done in 1933 and 1934, on the effect of estrogenic substances on experimental peripheral gangrene, and this work actually formed the foundation for the present clinical studies of the effect of estrogenic substances on the vasomotor instability usually observed in the early stages of thromboangiitis obliterans. Using ergotamine tartrate as a toxic agent and following the experiments of Rothlin (1923) and Polak (1928), one of us (McGrath) produced lesions of the peripheral arterial and venous pathways of the tail of the albino rat. These have been described previously.[5] Briefly, there resulted profound cellular proliferation and swelling of the intima, both arterial and venous, most pronounced in the smaller radicles on both sides of the vascular tree (fig. 1). In addition, marked thrombophlebitis and periphlebitis were observed.

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2. Albert, F.: Les oblitérations artérielles: Étude physio-pathologique, Lyon chir. **29**:649 (Nov.-Dec.) 1932.

3. Leriche, R., and Kunlin, J.: Traitement immédiat des phlébites post-opératoires par l'infiltration novocaïnique du sympathique lombaire, Presse méd. **42**:1481 (Sept. 22) 1934.

4. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, Surgery **5**:491 (April) 1939.

5. McGrath, E. J.: Experimental Peripheral Gangrene: Effect of Estrogenic Substance and Its Relation to Thrombo-Angiitis Obliterans, Arch. Int. Med. **55**: 942 (June) 1935; Experimental Peripheral Gangrene, J. A. M. A. **105**:854 (Sept. 14) 1935.

With the basic lesions established, parallel series of normal control animals, unprotected animals intoxicated with ergotamine tartrate and protected by daily administrations of estrone (theelin) were studied. It is sufficient to summarize the results. All the rats, male and female, unprotected by the estrogen and intoxicated with ergotamine tartrate had gangrene of the tail in greater or less degree, varying with the

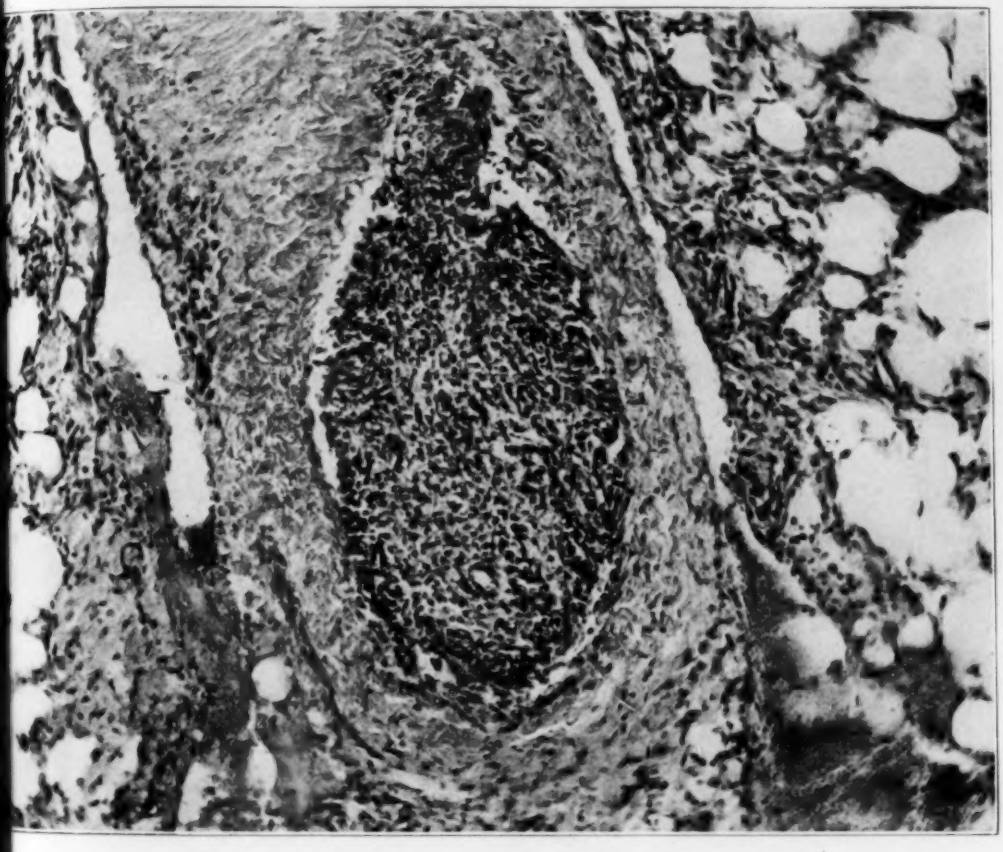

Fig. 1.—Cross section of the tail of an albino rat after intoxication with ergotamine tartrate. Note the thrombosis of the central artery. Magnification × 200.

amount of ergotamine employed (fig. 2). Conversely, female animals similarly intoxicated but protected with adequate estrogen did not have gangrene. Male animals, however, failed to respond to estrogenic therapy, becoming gangrenous in a fashion similar to unprotected males.

These results were corroborated by Suzman, Freed and Prag [6] in 1938, and the experiment was carried through the next logical step. Investigating the effect of castration on the male, these authors found that castration alone was inefficient in protecting the animals against ergotamine gangrene. However, it was found that administration of estrone to castrate male animals produced the same protective action that we had observed previously in female rats.

CHOLINERGIC ACTION OF ESTROGENIC SUBSTANCES

Markee [7] and Fagin and Reynolds [7a] demonstrated that when estrogen was injected into ovariectomized rabbits maximal hyperemia developed in the uterine tissues within thirty to sixty or more minutes. The little known fact, demonstrated by Pompen,[8] that the initial hyperemia

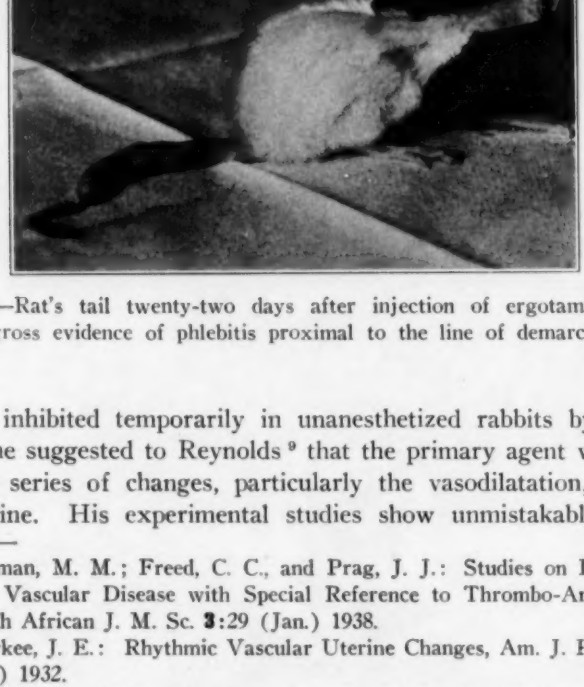

Fig. 2.—Rat's tail twenty-two days after injection of ergotamine tartrate. Note the gross evidence of phlebitis proximal to the line of demarcation of the gangrene.

could be inhibited temporarily in unanesthetized rabbits by injection of atropine suggested to Reynolds [9] that the primary agent which initiated that series of changes, particularly the vasodilatation, might be acetylcholine. His experimental studies show unmistakably that the

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7. Markee, J. E.: Rhythmic Vascular Uterine Changes, Am. J. Physiol. **100**: 32 (March) 1932.

7a. Fagin, J., and Reynolds, S. R. M.: Local Vascular Changes and Uterine Motility, Am. J. Physiol. **117**:86, 1936.

8. Pompen, A. W. M.: De invloed van menformon op der baarmoeder, Thesis, Amsterdam, 1933.

9. Reynolds, S. R. M.: The Cholinergic Action of Oestrin, Science **87**:537 (June 10) 1938.

acetylcholine content of the uterus was increased significantly within one hour after the injection of estrogen (amniotin). Since the effect occurred in a transplanted uterus, connection with the central nervous system is not essential, although in his experiments sufficient time had not elapsed for complete degeneration of the nerves. In the sense, therefore, that certain nervous effects on effector organs are mediated by local liberation of acetylcholine and accordingly are said to be "cholinergic," Reynolds [9] concluded that estrogen is similarly "cholinergic." Hence he concluded that this term must be broadened to include possible hormonal effects which are mediated peripherally by acetylcholine. In this way one could explain the maximal hyperemia which occurs experimentally in uterine transplants in which no nerves are demonstrated.[7] The high estrogen content associated with the high acetylcholine content of human placenta [10] in the complete absence of nerves could be explained also in that manner.

CLINICAL STUDIES

The results of these experimental observations encouraged us to study the clinical effects of estrogenic substances in patients with the active types of angiitis, much as Baecke and Sicard did in 1927. Our primary interest, however, centered around the effect of these substances on the vasomotor instability which is secondary to primary disease of the arteries or veins of the extremities. We had observed in previous clinical studies that occasionally the propagation of intravascular thrombosis with resultant spread of the pathologic changes in the walls of the arteries or veins was enhanced by slowing of the peripheral circulation due to widespread vasoconstriction; consequently we concluded that any lessening of irritability of the peripheral vasomotor system from within the organism might lessen the chance for extension of involvement of the peripheral vessels. Our clinical studies consisted mainly of repeated examinations of the peripheral vascular system before and after complete vasomotor relaxation in the "constant temperature room" (20 C.) to determine the kind and degree of changes in vasomotor control of the peripheral arteries and arterioles which developed during and after intensive treatment with estrogens.

The sustained effect of the estrogenic substances in this group of patients was found to come on slowly over a period of days, and little, if any, change in vasomotor function was ever detected in the hands or feet after administration of a single large dose or any series of smaller doses given over a period of hours. It has been shown that when estrogens are injected directly into the venous system they

10. Chang, Hsi Chun, and Gaddum, J. H.: Choline Esters in Tissue Extracts, J. Physiol. **79**:255 (Oct. 6) 1933.

rapidly disappear from the circulating blood. They must be injected, therefore, in such a way that absorption will take place slowly and the effect will be prolonged over a period of days. Much remains to be done in the study of estrogenic substances in relation to the maintenance of concentration of estrogen during several weeks or months. Daily injections of water-soluble preparations by no means approximate the normal secretion of estrogen. Considerable evidence exists that an effective level of concentration of estrogen can be best maintained by injection of an estrogenic substance in oil or in some other medium less rapidly absorbed than water. The rapid retrogression of hormonal effects on cessation of injections in the experimental animals and the rapid drop in excretion of estrogens after parturition indicate that there is little or no storage of these hormones in the body.

A distinct difference in response to estrogens has been noted in the male as compared with the female. Much more estrogen is needed, or administration must be carried over a longer period, to bring about clinical improvement in males. This is also true of the experimental studies on animals. The use of testosterone propionate for some male patients has given encouraging results, but further work will have to be done before any positive information concerning its use for this type of vascular problem can be presented.

OUTLINE OF THERAPY

In the management of all forms of arterial insufficiency in extremities, general measures for protection of the skin of the affected limbs against all forms of trauma, as advocated by Allen,[11] Reid [12] and others, must be considered of paramount importance. The serious complications which frequently follow in the wake of arterial insufficiency due to secondary vasospasm from any form of acute angiitis or phlebitis in the extermities are usually precipitated by some form of physical, chemical or thermal trauma to the affected parts.

We have employed an oily preparation of estrone (ampules theelin in oil, Parke, Davis & Co.) and have administered it intramuscularly to all patients included in this study. During the early part of our clinical work we used relatively small amounts of the estrogen (2,000 international units) at weekly intervals, but later studies showed that a more sustained effect followed prolonged administration of larger amounts. At present we are giving 4,000 international units of theelin (estrone) twice each week for four weeks and then 4,000 international units

11. Allen, A. W.: The General Management of Circulatory Disorders of the Extremities, New England J. Med. **204**:859 (April 23) 1931.

12. Reid, M. R.: The General Care of Peripheral Vascular Diseases, Ann. Surg. **96**:733 (Oct.) 1932.

once each week for the subsequent twelve weeks. This amount given in sixteen weeks has been designated in this work as a course of treatment.

All of our patients were taught how to care for the skin of their hands and feet and how to protect them from all forms of trauma. Abstinence from the use of tobacco in all forms was considered essential. About half the patients had stopped smoking on the advice of other physicians weeks or months prior to the beginning of treatment with estrogenic substances. The others stopped smoking at the beginning of the first course of treatment with estrone (theelin) therapy. An attempt was made to remove as many of the exogenous factors as possible before the active treatment was started.

A rest of from two to six months is prescribed, during which time all the other measures of general care are carried out and the extremities are protected from the cold at all times. Patients are permitted to be moderately active but are cautioned about overfatigue. They are instructed to return for regular follow-up examination and study.

ANALYSIS OF CLINICAL RESULTS

As the basis for this report, a series of 16 patients with arterial insufficiency due to secondary vasomotor instability associated with active arteritis or phlebitis were studied and then treated by parenteral administration of moderate quantities of estrogen (estrone, or theelin) at regular intervals for at least sixteen weeks.

It is extremely difficult to evaluate properly all the changes which occur as the result of any therapeutic agent or regimen, especially when one is dealing with disease processes which are known to show periods of spontaneous remission as well as of spontaneous exacerbation and which have been shown to be influenced by a variety of exogenous and environmental factors.

All the patients referred to in this report have been studied at regular intervals, and the final decision as to the condition of the patient was based on the results of objective studies of the efficiency of the peripheral vascular system and on analysis of the patient's account of the effects on the signs and symptoms of a variety of different environmental conditions.

A summary of the data concerning the 16 patients of this series is given in table. 1. Two women and 1 man showed marked secondary vasospasm in the lower extremities, due to acute thrombophlebitis. No attempt has been made to differentiate between men with active migrating phlebitis and those with early thromboangiitis obliterans, since marked secondary vasoconstriction was associated with both types of processes.

Pain was pronounced in 12 of the patients, and these were given moderately large amounts (50 mg. intravenously each day for five days) of thiamin chloride (vitamin B_1) in addition to the estrogenic substances.

We have not attempted to make any correlation between the number of international units of estrone (theelin) administered and the degree of improvement which followed the treatment. All of the

TABLE 1.—*Data on Patients with Secondary Vasomotor Instability in the Extremities Before Treatment with Estrogenic Substances*

Statistical Information					Signs			Symptoms		
Patient	Diagnosis	Age	Sex	Parts Affected	Pallor	Cyanosis	Rubor	Pain	Numbness	Tingling
1	T. A. O.*	29	M	Feet	++++	++	+++	++++	+++	+++
2	T. A. O.	27	M	Feet	++++	++	++++	++++	+++	+++
3	T. A. O.	27	M	Hands and feet	++++	+++	++	++++	+++	+++
4	T. A. O.	41	M	Feet	++	+++	++++	++++	+++	++++
5	Phlebitis	25	F	Feet	++++	+++	0	++++	+++	++
6	T. A. O.	24	M	Feet	++++	++	+	+++	++	+
7	T. A. O.	41	M	Feet	++++	++	++	++	+++	+++
8	T. A. O.	30	M	Fingers	+++	+++	0	++++	++	+++
9	T. A. O.	34	M	Feet	++++	++	0	++++	+++	+++
10	Arteritis	52	M	Fingers	++++	++++	++	++++	++++	+++
11	Phlebitis	40	F	Feet	++++	++	0	++++	++	+
12	T. A. O.	46	M	Feet	++++	+++	++++	++++	+++	++
13	T. A. O.	19	M	Feet	++++	++	+++	++	++++	++
14	T. A. O.	42	M	Feet	+++	++	0	++	+++	++
15	Phlebitis	48	M	Feet	+++	++	0	++	+++	++
16	Thrombosis	30	F	Fingers	++++	++++	0	++++	++++	++++

* Thromboangiitis obliterans.

TABLE 2.—*Clinical Results of Treatment with Estrogenic Substances*

	Patient No.*																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Percentage
Improved	+	+	+	+	+	..	+	..	+	..	+	+	+	..	+	..	±69
Unchanged	..	..	..	..	..	+	..	..	..	+	..	..	..	+	..	+	±25
Worse	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	± 6

* Same patients as in table 1.

patients listed as improved have been able to return to their work. Either the vasomotor instability completely disappeared, or the disease process remained so quiescent that the patient was caused no great disability or concern. Vascular studies of these patients showed a more nearly normal vascular response under natural environmental conditions as well as under the controlled conditions (normothermia) in the constant temperature room.

Of these 16 patients, 11, or 69 per cent, definitely were improved (table 2). The signs of vasomotor instability in the digits became much less marked. The pain in the digits showed corresponding

improvement, and the disability was reduced to a negligible level in most cases. In 3 patients recrudescence of the signs and symptoms occurred after two years of relief, but the activity of the process again subsided, although less completely, after another course of treatment with the estrogenic substances. In 4 patients, or 25 per cent, the symptoms have remained unchanged after many months of observation. In 1 patient, or 6 per cent, the symptoms continued to grow worse in spite of all our therapeutic effort.

SUMMARY

A total of 16 patients with marked secondary vasoconstriction associated with active angiitis in the extremities has been studied and then given estrogens as the primary therapeutic agent. In this review of our experiences, an attempt has been made to present our interpretation of the benefits which have resulted after a careful analysis of the patient's account of the subjective benefits together with the objective evidence of importance we have gathered from repeated vascular studies. It must be emphasized that 3 patients of this series who had active thromboangiitis obliterans have returned after several years with reactivated acute angiitis.

The cholinergic effect of the estrogenic substances appears to supply only a partial explanation of these clinical results. What other effects may be exerted on the diencephalic vasomotor centers through the primary effect of the estrogenic substances on pituitary function is a problem for further study. It is a clinical fact, however, that all patients do not react alike to these substances, and the apparent difference between the reaction of the male organism and that of the female might be explained on the basis of less intense action on the central vasomotor centers. We simply wish to record, without further comment, these moderate differences in reaction between males and females and between males of different constitutional makeup.

We do not wish to draw any conclusioins from the study of such a small series of patients presenting such varied clinical syndromes; nevertheless, after making these studies, we can see that the problem is worthy of more careful study and thought, and we believe that in this conclusion lies whatever value there may be in the present report.

SPEED OF BLOOD FLOW IN THE ARTERIES AND IN THE VEINS OF MAN

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Methods used since 1922 for determining the speed [1] with which blood flows in man depend for the most part on production of a reaction in one part of the body (for example, the tongue) to a substance injected into a vein in another part of the body (for example, the median basilic vein). The time elapsing between injection of the substance and detection of the reaction is known as circulation time.

Substances used are potassium ferrocyanide,[2] an active radium deposit,[3] calcium salts,[4] magnesium sulfate,[5] dehydrochloric acid,[6]

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1. The term "speed" lacks accuracy, but its use is justified by convenience. If used accurately, it must embody two measurements, distance and time. In our studies no measurements of distance were made, but since those distances studied are roughly equal among different patients and since the term "speed" can be used much more conveniently than other more nearly accurate ones, it has been used advisedly in this presentation.

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6. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion (Kurze Mitteilung), Med. Klin. **27**:986-988 (July 3) 1931. Gargill, S. L.: The Use of Sodium

saccharin,[7] various dyes,[8] ether,[9] histamine[10] and sodium cyanide.[11] These substances have been used chiefly for determining the speed of blood flow in a pathway consisting of peripheral veins, pulmonary arteries and veins, chambers of the heart and part of the arteries originating from the left ventricle. The circulatory pathway from the arm to the tongue is a good example. Because a solution[12] containing magnesium sulfate, calcium gluconate and sodium chloride produces a sensation of warmth in the extremities when it is injected

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intravenously, we have used such a solution in an attempt to estimate the speed of the flow of blood in peripheral arteries. Because a solution of sodium cyanide [11] when injected intravenously produces a sudden gasp by action on the carotid sinus, we have used such a solution to estimate the speed of blood flow in peripheral veins. It is our purpose in this paper to report the results of these studies.

TECHNIC

Use of a solution containing magnesium sulfate, calcium gluconate, sodium chloride and copper sulfate, which was introduced by Spier, Wright and Saylor,[12b] has been discussed by them and by two of us (Kvale and Allen [12a]). When this solution is injected intravenously, it produces a sensation of warmth in the tongue (or throat), perineum, hands and feet of the subject. The subject is informed of the type of reaction he is to experience and is instructed to report immediately the site of the sensation by saying "tongue," "crotch," "hands" or "feet," according to the region in which the first sensation arises.[13] When the sensation occurs in the hands, it usually occurs in the two simultaneously. The same usually is true of the feet. However, the sensation may occur in one hand before it does in the other and in one foot before the other, and in such cases the subject designates the site by saying "right hand" or "left hand" and "right foot" or "left foot."

The subject is supine in bed, with the arm at the level of the heart. A tourniquet is applied. Two cubic centimeters of the solution is drawn into a 3 cc. syringe which has been fitted with a 20 gage needle. The needle is then inserted into a vein overlying the antecubital fossa, the tourniquet is removed, and after three to five seconds the solution is injected as rapidly as possible. When the injection is started, the person performing the test says "Go," and an assistant starts the stopwatch. The circulation time is recorded as the subject calls out the various places at which the sensation is perceived. The time elapsing between the beginning of injection of the solution into a vein at the elbow and the occurrence of the sensation of warmth in the throat, perineum, hands and feet is determined. We do not know that occurrence of the sensation of warmth in the hand, for instance, indicates that the solution has concurrently arrived at the hands, but for the purpose of simplification we have assumed that this reasoning is correct. The expressions "arm to hand" and "arm to foot" indicate the time elapsing between the beginning of the injection into a vein at the elbow and the sensation of warmth in the hands and in the feet respectively. Occasionally subjects have been unable to perceive the sensation; in such cases the term "blank" has been used. Such a study as the present one does not allow determination of the velocity of the flow of blood in the arteries, for there is no way of knowing when the solution leaves the left ventricle. However, this can be estimated with reasonable accuracy. By the time the solution reaches the tongue from the left ventricle, it probably has traversed the aorta for a distance equal to that traversed to the tongue. The time required for the blood to traverse this distance appears to be about one second, although this has not been accurately established. Because this time is relatively constant and relatively short, we have eliminated it from our calculations and have assumed that when the sensa-

13. It seems worth while to emphasize that in this paper a decrease in circulation time indicates an increased velocity of blood and that an increase in circulation time indicates a decreased velocity of blood.

tion of warmth occurs in the tongue the solution is leaving the left ventricle. We therefore estimate the circulation time from the left ventricle to the perineum by subtracting the "arm to tongue time" from the "arm to perineum time." The "ventricle to hand time" [14] is calculated by subtracting the "arm to tongue time" from the "arm to hand time"; the "ventricle to foot time," by subtracting the "arm to tongue time" from the "arm to foot time." The figures thus obtained are subject to the qualification which we have noted. They afford us, for the first time, approximately correct figures for determining the speed of blood flow in peripheral arteries.

In studying the venous circulation time it was desirable to use a method which was simple, easily performed and objective. Injection of measured quantities of 2 per cent sodium cyanide solution was made in the antecubital veins and in the veins of the foot or ankle. The time as measured by a stopwatch between the beginning of the injection and the occurrence of a sharp respiratory stimulation constituted the circulation time from the point of injection by the shortest pathway to the carotid sinus.

NORMAL CONDITIONS

With normal subjects, the average for 87 determinations of the "arm to carotid sinus time" (with sodium cyanide) was twenty and eight-tenths seconds. The average for 102 determinations of the "arm to tongue time," (with the solution of calcium, magnesium and sodium salts) was thirteen and seven-tenths seconds. When the two solutions were mixed it was found that sensation was perceived in the tongue at an average of three and one-half seconds before a gasp resulted from stimulation of the carotid sinus by the sodium cyanide. We have concluded that there is an error inherent in the sodium cyanide method and that values obtained by such a method are approximately three and one-half seconds greater than they should be. The average figures for other circuits follow: arm to perineum, twenty-one seconds; arm to hand, twenty-three and one-half seconds; arm to foot, thirty-two seconds; ventricle to perineum, seven and three-tenths seconds; ventricle to hand, nine and eight-tenths seconds; ventricle to foot, eighteen and a half seconds, and foot to carotid sinus, thirty-nine seconds.

CHRONIC OCCLUSIVE ARTERIAL DISEASE

A study of 28 cases of thromboangiitis obliterans and arteriosclerosis obliterans indicates that when a subject has these diseases the average time required for blood to flow to the feet is increased (the approximate mean "ventricle to foot time" for subjects with these conditions was twenty-four seconds, as contrasted with a normal value of eighteen and one-half seconds). However, in individual instances of chronic occlusive arterial disease the circulation time seemed normal. Therefore, tests of the speed of arterial circulation cannot be employed in arriving at diagnoses of chronic occlusive arterial diseases.

14. Throughout the paper the term "ventricle," used as it is used here, refers to the left ventricle.

HYPERTHYROIDISM

The speed of blood flow is increased in the presence of hyperthyroidism. In thirty-one tests of 14 patients with the condition the average circulation time from the arm to the tongue was ten and four-tenths seconds; from the ventricle to the perineum, four and six-tenths seconds; from the ventricle to the hand, about six seconds, and from the ventricle to the foot, about eleven seconds. These periods are shorter by approximately three, three, four and seven seconds respectively than those observed in similar tests of normal subjects. Administration of 4 to 6 grains (0.26 to 0.4 Gm.) of desiccated thyroid substance daily for four days changed the average "foot to carotid sinus time" from forty to twenty-nine seconds and the average "arm to carotid sinus time" from twenty to sixteen seconds.

ESSENTIAL HYPERTENSION

The speed of blood flow in patients with uncomplicated essential hypertension agrees with that in normal subjects. The average values, determined by a study of 37 subjects, follow: arm to tongue, fourteen and four-tenths seconds; arm to perineum, twenty-two seconds; arm to hand, twenty-three seconds; arm to foot, thirty-six and one half seconds; ventricle to perineum, seven and one-half seconds; ventricle to hand nine seconds, and ventricle to foot twenty-one and one-half seconds. These all may be considered normal except the circulation time from the arm to the foot and that from the ventricle to the foot, which are about four and one-half and three seconds greater respectively than similar averages for normal subjects, an observation which suggests slowing of the flow of blood to the lower extremities in the presence of essential hypertension.

EFFECT OF SYMPATHECTOMY

If sympathectomy affecting one extremity has been performed as part of the first stage operation for relief of essential hypertension, the average circulation time from the ventricle to the sympathectomized foot is nine seconds less than for the opposite, unsympathectomized extremity (twenty-five and one-half seconds). The average "foot to carotid sinus time" is thirteen and seven-tenths seconds less for the sympathectomized limb than for the normal, unsympathectomized companion member (forty-four and seven-tenths seconds). Results of these studies indicate that lumbar sympathectomy performed as a part of the operative treatment for essential hypertension increases the speed of blood flow in both arteries and veins and that vasodilatation results from sympathectomy. Two other observations are of interest. After both limbs had been sympathectomized, the circulation time for the

limb that had been sympathectomized first was increased as compared with that observed after the original operation. After both operations had been performed, the venous circulation time was less for the more recently sympathectomized limb than for that originally sympathectomized. These observations suggest that there is a gradual recovery of vascular tone in limbs to which the sympathetic fibers have been cut.

EFFECT OF TEMPERATURE OF THE SKIN OF THE EXTREMITIES

The temperature of the skin was determined with an electric thermometer. Changes in temperature of the skin were produced by various methods, such as moving the patient from a room the temperature of which was constant at 18 C. into a room the temperature of which was constant at 25 C., by placing a "baker" over one extremity and producing vasodilatation and by placing a "baker" over the entire body, producing generalized vasodilatation. The rate of circulation in the peripheral arteries was always increased when the temperature of the skin was increased and decreased when the temperature of the skin was decreased. For example, in 1 instance the "arm to foot time" was forty-nine seconds when the temperature of the skin of a toe was 29.5 C. and thirty-seven seconds when the temperature of the skin of a toe was 38 C. This observation emphasizes the need for controlled conditions, constant room temperature and a fasting state in determining the speed of circulation. Not infrequently when tests were performed with the solution of calcium and magnesium salts it was noticed that "blanks" occurred, that is, that the subject failed to perceive the sensation of warmth in the extremities. Some of these "blanks" were the result of confusion on the part of the subject, but many were the result of the fact that the cutaneous temperature of the extremity was relatively low. When the cutaneous temperature was increased, the subject perceived the sensation distinctly.

Our studies show that when the skin is cool the circulation time from the foot to the carotid sinus is increased, and that when the skin is warm it is decreased. For example, in 1 case, when the temperature of the skin of a toe was 20.7 C., the "foot to carotid sinus time" was forty-nine and four-tenths seconds, and when the temperature of the skin of a toe was 32.6 C., it was twenty-five and four-tenths seconds. These observations indicate that the temperature of the skin is most important in determining the speed of the flow of blood in veins.

EFFECT OF POSTURE

It was desirable to know the effect of elevation of the extremities on the circulation time from the arm to the carotid sinus and on that from the foot to the carotid sinus. Values for the former with the

vein at the level of the right auricle were compared with values obtained when the arm was supported at an angle of 30 degrees with the horizontal. The same procedure was used in testing the effect of elevation on the circulation time from the foot to the carotid sinus. Decrease of "arm to carotid time" by 12 to 20 per cent and of "foot to carotid time" by 8 to 25 per cent are the results of elevation of the extremity, results which mean that venous blood flows more rapidly in an elevated extremity than in one which is horizontal. The circulation time from the ventricle to the foot was increased in almost all instances when the subject stood. In other words, arterial blood appears to flow more slowly in the legs when a subject is upright than when the subject is recumbent, a result which may be caused by orthostatic vasoconstriction in the lower extremities.

EFFECT OF DIGESTION

Studies were performed on subjects who had fasted and were repeated about two hours after the subjects had ingested a large meal. When the temperature of the skin of the digits increased as a result of digestion, the blood nearly always flowed faster. For example, in 1 instance, when the temperature of the skin of the toes increased from 27.3 to 32.8 C. as a result of digestion the "arm to perineum time" decreased from twenty-six to nineteen seconds; the "arm to hand time," from thirty-two to twenty-five seconds, and the "arm to foot time," from forty-six to thirty-five seconds.

EFFECT OF EXERCISE

A standard set of exercises was used, with the subject supine to reduce the effects of other factors. Control values for the circulation time from the foot to the carotid sinus and from the arm to the carotid sinus were obtained and were redetermined within two minutes after cessation of the movements. Speeding of the flow of blood uniformly occurred in the legs after exercise. The reduction in "foot to carotid sinus time" ranged from 24 to 40 per cent. The circulation time remained the same after exercise of the arms in 1 subject and was even slowed in 3.

The test for circulation time from the arm to the foot was performed first when the subjects were at rest and next after the subjects had ascended and descended a set of steps for one minute, after which the pulse rate was accelerated to as low a figure as 104 and to as high a figure as 140. In almost all instances the speed of blood flow in the peripheral arteries was found to be increased after exercise. For example, in 1 instance the "arm to tongue time" decreased three seconds, the "arm to hand time" three seconds and the "arm to foot time" ten seconds.

These observations show that exercise increases the speed of flow of blood in both arteries and veins.

EFFECT OF OPERATION

The effect of operation on venous circulation time was studied in a group of 31 patients, 21 men and 10 women. With all of these patients circulation time was obtained under standard conditions before operation. With 9 patients studies were made at intervals varying from two hours to ten days after the operation. The remaining 22 patients were tested at intervals varying from two to thirteen days after the operation.

Twenty-four hours after the operation, the circulation time from the arm to the carotid sinus was decreased in all instances. After the second postoperative day there was some increase of circulation time for 48 per cent of the patients, a decrease for 32 per cent and essentially no change for 20 per cent. The only distinct change in the circulation time from the arm to the carotid sinus after operation was a definite decrease during the first forty-eight hours.

Two days after the operation the average circulation time from the foot to the carotid sinus increased from its first postoperative decrease. Beginning on the fifth postoperative day, it became progressively greater until the eighth to the thirteenth postoperative day. Study of the individual patients revealed that for 82 per cent there was distinct increase, for 11 per cent a decrease and for 7 per cent essentially no change.

These observations, which will be reported in detail in the future,[11b] indicate that the speed of blood flow in the veins of the legs is usually reduced by operation. The possible relation of this observation to postoperative thrombosis and embolism will be discussed in a subsequent publication.

SUMMARY AND CONCLUSIONS

The methods of study which we have used indicate that the speed of the flow of blood in the arteries and in the veins of the extremities is influenced by a number of factors. Chronic occlusive arterial diseases usually slow the arterial circulation but do not always do so. Hyperthyroidism increases the speed of blood flow; hypertension slows it in the lower extremities; sympathectomy speeds it greatly, as does increasing the temperature of the skin of the digits. Elevation of an extremity increases the speed of flow of venous blood, but when the subject stands the speed of flow of arterial blood is decreased. Digestion is associated with an increase in speed of blood flow, and exercise accelerates flow in arteries and veins. Operation usually reduces the speed of the flow of blood in the veins of the lower extremities.

DIABETIC GANGRENE

REVIEW OF NINE HUNDRED AND SEVENTY-TWO CASES OF GANGRENE ASSOCIATED WITH DIABETES MELLITUS TREATED AT THE NEW ENGLAND DEACONESS HOSPITAL

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In this paper I shall try to give a general picture of the diabetic patient with gangrene, to describe the organization for and the principles of management of cases of diabetic gangrene at the New England Deaconess Hospital and possibly, through a study of my results, to indicate how I have arrived at my present conception of the operative treatment of this condition. I do not wish to add to the many reports on the details of management of diabetic gangrene or to enter into any controversy as to the indications for amputation or the level at which it should be done.

ORGANIZATION FOR THE CARE OF "SURGICAL DIABETIC" PATIENTS AT THE NEW ENGLAND DEACONESS HOSPITAL

I did my first amputation for gangrene—a closed amputation through the upper third of the lower part of the leg—in May 1923. Insulin had been given to the first patient in the New England Deaconess Hospital the preceding August and had already completely changed the outlook for the diabetic patient in need of surgical treatment. Coma, no longer a fatal complication, had been replaced by gangrene as one of the most frequent causes of death.[1]

My interest in the surgical complications occurring in patients with diabetes was encouraged by the late Dr. D. F. Jones, to whose early concepts of the management of such conditions subsequent years and increasing experience have added little. Through the interest and generosity of Dr. Elliott P. Joslin, every opportunity was given to develop facilities for the study and care of patients with diabetic gangrene at the New England Deaconess Hospital. When the many time-consuming details necessary for the proper care of the patient and the importance of teaching hygiene of the foot were recognized, a graduate nurse was

1. Morrison, in his study of 775 deaths in Boston, had previously shown that in 23 per cent of these gangrene was a contributory cause (Morrison, H.: Boston M. & S. J. **175**:54, 1916).

obtained and was given special training in the technic of surgical dressings and in prophylactic care of the foot. The "beauty parlor for diabetic feet" was thus established. Here the patient was not only told but taught to "keep his feet as clean as his face." It was soon found that more and more responsibility could be given the nurse in the actual dressing of the smaller "surgical" wounds. Thus the surgeon was relieved of many of the details of minor but important and time-consuming dressings. This confidence was more than justified, and as the number of patients increased it became necessary to give the nurse an assistant. The present organization, therefore, consists not only of the surgical and medical components of the team but, in addition, of two especially trained graduate nurses whose entire time is devoted to the actual care of surgical dressings under the direct supervision of my associate Dr. T. C. Pratt and me.

Early in 1924, regular weekly ward rounds were instituted at the suggestion of Dr. Joslin. Promptly at 8 a. m. each Monday, Dr. Joslin, his assistant, Dr. Howard F. Root, Dr. D. F. Jones, the nursing personnel directly responsible for the medical and surgical care of the diabetic patients and I met in the ward. Each surgical patient was seen; all the dressings were removed, and the wounds were examined. The medical and surgical problems of each patient were discussed. Questions relating to individual patients were brought up and decisions made. New advances, either medical or surgical, were presented to the group for deliberation. Throughout the period of approximately fourteen years it is doubtful that this visit has been omitted more than once a year. Its permanence is evidence of its importance and value as a common ground for surgical and medical intercourse in the management of this difficult condition.

To assure accurate data, a special surgical card is used, on which are placed the pertinent facts in relation to each case as the patient is admitted to the hospital. Postoperative notes are added at the time of discharge, and additional space is left for follow-up notes. It is from these cards that this and other, similar studies have been made.

RÉSUMÉ OF CASES FOR STUDY

Between May 1923 and Jan. 1, 1939, 972 patients have been seen and treated for obliterative arterial disease and diabetes mellitus.

During the same period, 319 patients have been operated on for infection of a lower extremity, but careful evaluation of the arterial supply of these patients has convinced my associates and me that, although not normal, it was adequate. Their cases, therefore, as suggested by Coller and Marsh,[2] should not be included in a discussion of cases of diabetic gangrene.

Sex.—In this series, the incidence of gangrene was about equally divided between men and women. Fifty-three per cent of our patients were women, slightly less than the ratio of women (57 per cent) in Joslin's [3] series.

Age.—The average age of all our patients was 64.3 years, that of the women (65.2 years) being a little greater than that of the men (63.8 years).

Duration of Diabetes.—The patients had had diabetes for an average of eight and seven-tenths years. The difference between the average duration for the women (nine and three-tenths years) and that for the men (eight and six-tenths years) is not significant.

It seems fair to say, then, that the average patient with diabetic gangrene may be either a man or a woman, is about 64 years old and has had diabetes for an average of about eight and a half years.

TABLE 1.—*Nine Hundred and Seventy-Two Cases of Incipient or Actual Gangrene in Patients with Diabetes Mellitus (New England Deaconess Hospital, 1923-1939)*

Treatment	Number	Deaths	Mortality, per Cent
No operation*	414	19	4.6
Minor amputation	63	4	6.3
Major amputation	495	69	13.9
Total	972	92	9.5

* Patients treated without operation prior to 1930 not included.

ADMISSION ROUTINE FOR SURGICAL PATIENTS

At the New England Deaconess Hospital there is no distinction between the medical and the surgical wards. Promptly after examination of the patient on admission the surgical consultant is called, and the patient is seen by Dr. Pratt or by me within a few hours. Surgical treatment is instituted at once; antidiabetic treatment already will have been started. If operation is indicated, the time at which it will be done is based primarily on the urgency of the local condition. In our earlier experience many of these conditions were treated as emergencies, and amputation was done on the day of admission. Although we still consider them emergencies in that they should be seen by the surgical consultant promptly after admission of the patient, increasing experience

2. Coller, F. A., and Marsh, P. L.: Lesions of Extremities Associated with Diabetes Mellitus, J. A. M. A. **85**:168 (July 18) 1925.

3. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 139.

has shown us that it is only the occasional case in which immediate operation is needed and that sufficient delay to permit adequate fluid intake and adjustment of the metabolic imbalance is desirable. Moreover, in some cases of gangrene with active infection a waiting period of twenty-four to seventy-two hours is frequently of great help in determining the type of operation indicated. This is in keeping with the conclusions of Maes,[4] who found that the safest time for operation is after two or three days of preparation. Since the introduction of chemotherapy, there are a few cases in which forty-eight or seventy-two hours of adequate sulfanilamide intake may make the difference between a guillotine amputation and a primary closed amputation. However, most of the patients whom we see with actual gangrene due to obliterative arterial disease have a lesion badly contaminated with a variety of organisms, the beta hemolytic streptococcus in our cases playing a relatively minor role. We cannot but feel that Meleney[5] placed rather more stress on the bacteriologic factor in diabetic gangrene than our experience would justify.

TECHNICAL CONSIDERATIONS AND RESULTS

Approximately half the patients who come under treatment are treated without operation. Eleven and three-tenths per cent of the others have a successful amputation of one or more toes, and 88.7 per cent have a major amputation. Thirty-three patients have refused amputation and have gone elsewhere for treatment. These will be discussed later in this paper.

Level of Amputation.—The indications for operation and the factors from which the level of amputation is decided were first outlined in 1928[6] and have been reviewed more recently.[7] In 1923, amputation through the lower part of the leg was most frequently done. During the past sixteen years, waves of enthusiasm have increased temporarily the number of amputations below the knee or the number of Gritti-Stokes amputations, but throughout this period there has been a gradual but steady trend in favor of the supracondylar amputation. As one looks at table 2 and notes the small number of amputations through the lower part of the leg in proportion to the number of those above the knee, one cannot but wonder at the sequence

4. Maes, U.: Personal communication to the author.

5. Meleney, F. L.: Surgery **6**:845, 1939.

6. McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.

7. McKittrick, L. S.: Am. J. Surg. **44**:46, 1939.

of events which has resulted in gradual elimination of other levels of amputation in favor of the supracondylar operation. It is possible that with the latter there are a few patients who have been unjustly denied the tremendous advantage of a knee joint. A careful study of our results, however, not only in the immediate management of the patients but after they have left the hospital, has convinced us that except in selected cases the operation which is the safest and is followed by the

TABLE 2.—*Results After Operation for Gangrene*

Operation	No.	Deaths	Mortality, per Cent	Wound Healing: Healing by First Intention	Wound Healing: Sepsis: Major	Wound Healing: Sepsis: Minor	Wound Healing: Sepsis: Unstated	Postoperative Stay in Hospital, Days
Amputation of toe	63	4	6.3	2	(Granulation, 61)			46
"Lower leg" amputation	42	2	4.8	7	4	13	18	41
Guillotine amputation*	37	13	35.1	...	..	..	...	..
Gritti-Stokes amputation	104	15	14.4	28	12	15	49	51
Supracondylar amputation	330	38	11.5	165	18	33	114	29
Death under anesthesia	1	1	100.0	...	..	..	...	..

* Nineteen guillotine amputations followed by amputation at a higher level are classified also under the secondary level at which amputation was done.

TABLE 3.—*Comparison of Results with Silk and Catgut in One Hundred and Twelve Consecutive Primary Thigh Amputations*

	Number	Healing by First Intention	Sepsis: Major	Sepsis: Minor	Sepsis: Not Stated	Postoperative Stay in Hospital, Days
Catgut						
1939	31	30	0	0	1	17.4
1938	23	20	0	1	2	21.3
1936	2	1	0	1	0	18.5
Total	56	51 (90.2%)	0	2 (3.8%)	3	19.4
Silk						
1936	27	16	0	3	8	20.0
1937	29	23	0	1	5	27.1
Total	56	39 (90.7%)	0	4 (9.3%)	13	23.5

shortest and easiest convalescence is the procedure of choice. This, according to our experience, is the supracondylar amputation (tables 2 and 3).

Drainage of Stump.—Dr. Jones was an early advocate of the circular amputation for a patient with obliterative arterial disease. He insisted particularly that if the amputation is carefully done and the fascia sutured over the end of the bone without undue tension, the insertion of a drain is of no value and in most instances is a definite hazard. As a house officer at the Massachusetts General Hospital before this teaching

had been accepted by the other members of the staff, I followed a number of amputations in which drainage had been used. Later, as assistant to Dr. Jones, I helped him with similar cases in which the wounds were carefully and completely closed. I was easily convinced then, and subsequent experience has confirmed the soundness of his judgment. In every case in this series, either a guillotine amputation has been done without any sutures or the wound has been closed without drainage.

Treatment of the Nerves.—Until 1930, absolute alcohol as advocated by Huber and Lewis [8] was injected into the nerve trunk. It was difficult to prevent some leakage of alcohol from the cut nerve. This made little, if any, difference in the center of a large thigh stump, but the common peroneal nerve is very close to the incision in a Gritti-Stokes amputation, and a little leakage may easily result in an area of necrosis of the stump. The use of alcohol was therefore discontinued; the nerve was crushed and tied (Little [9]) to avoid hemorrhage from the accompanying vessels, and the end was cauterized as advocated by Hedri.[10] In our opinion, either is satisfactory; we have had but one readmission to the hospital for a painful stump, and in this instance the pain was not sufficiently severe to warrant any active treatment. It is our impression that the particular group of patients under discussion will do perfectly well without any special treatment of the nerves, provided early healing without infection occurs.

Sutures.—With the more recent controversy concerning the relative merits of silk and catgut, it seemed to us only a matter of time before silk sutures would be advocated as the answer to problems of wound healing in amputations for gangrene. Beginning in 1936, therefore, and continuing through 1937, fine silk was used in all amputations. We have selected cases of primary thigh amputation for comparison because we know of no other group of cases in which other factors are as constant as in this. These operations have all been done by Dr. Pratt or myself. I doubt that our technic has improved much, if any, during the past few years. We have not altered our conception of the indications for operation, the level at which amputation is done or the technic which has been used. In other words, as nearly as is clinically possible all factors except suture material are constant.

Table 3 shows comparative studies of results obtained from the use of silk and from the use of catgut. No. 1 chromic catgut was

8. Huber, G. C., and Lewis, D.: Amputation Neuromas: Their Development and Prevention, Arch. Surg. **1**:85 (July) 1920.

9. Little, E. M.: Artificial Limbs and Amputation Stumps, Philadelphia, P. Blakiston's Son & Co., 1922, p. 36.

10. Hedri, O.: Arch. f. klin. Chir. **253**:118, 1921.

placed around the popliteal artery in both series, because a large suture is necessary to crush the calcified walls of the artery. No. 00 plain catgut was used for the smaller vessels, and the fascia was approximated with no. 00 chromic catgut. Nonboilable sutures were used. In the "silk series," nos. 3 and 5 untreated black twisted silk were used for the smaller vessels and for fascia.

In order to be classified as healing by first intention, the wound must be solidly healed and the sutures removed within twelve days. There must have been no separation of the edges of the skin, no necrosis and no suppuration around any of the sutures; the stump must not have been red, and there must have been no serum. A stump is credited with healing by first intention only when a note has been made on the surgical card to that effect. However, cases listed in the table in which a definite note was not made probably were cases in which healing occurred by first intention, since in most if not all of them the stump was recorded as healed at the time of discharge.

We realize that this group of cases is small. On the other hand, it is our clinical impression, and from a study of this small group of cases I believe we are justified in assuming, that in a supracondylar amputation for gangrene neither suture material holds any merit over the other so far as wound healing is concerned, provided that the suture used is only large enough to permit careful approximation of the fascia. Needless to say, it is gratifying to us to find that the wounds in 96 per cent of our cases of primary thigh amputation for gangrene heal so promptly and that there has been no deep infection in the stump after such an amputation during the past four years.

Duration of Stay in the Hospital.—It has been our constant endeavor to select as accurately as possible the patients for whom major amputation is necessary; to do the operation as soon as the decision can be made, and to discharge the patient as early as is consistent with his welfare (table 4). The importance of the economic problem presented by diabetic persons with gangrene cannot be minimized. Two months of hospitalization is not too much to spend for a useful foot, but the unsuccessful attempt should, if possible, be recognized early and amputation at a higher level promptly carried out.

Patients who after major amputation are not going to use an artificial limb are discharged twelve to fourteen days after the operation. Patients who offer some possibility of using an artificial limb are fitted with a temporary appliance toward the end of the second week of their stay in the hospital and during the third week are taught the fundamental principles of using a peg leg.

Comparison of the length of stay in the hospital after thigh amputations (tables 2 and 3) shows how this period has been gradually shortened.

Bilateral Amputations.—We have done 70 bilateral amputations. This represents 16 per cent of our cases. The true incidence of bilateral gangrene will be shown later to be about 40 per cent. The average interval between discharge from the hospital and the onset of gangrene of the other leg was twenty-five and three-tenths months, which is comparable to the twenty-seven and six-tenths months to be mentioned (table 7). It is interesting to find that the result following operation

TABLE 4.—*Duration of Stay in Hospital*

Type of Treatment	Preoperative Period, Days	Postoperative Period, Days	Total, Days
No operation	..	..	23
Minor amputation	17	46	63
Primary major amputation	8	26	34
Multiple operations for the same lesion	16	49	65

TABLE 5.—*Causes of Death After Amputation for Gangrene*

Cause		Number	Per Cent
Infection		29	39.7
Cardiorenal disease		29	39.7
Pulmonary disease		13	17.8
Bronchopneumonia	6		
Embolism	7		
Miscellaneous		2	2.7
Total		73	

on the remaining extremity is definitely better than that following the first operation. Not only is life expectancy increased, but the risk of operation is less. Six, or 8.6 per cent, of the 70 patients died in the hospital after amputation of the remaining limb, as compared with the mortality of 13.9 per cent for all major amputations. It is of interest too that the total period of hospitalization for a patient admitted to the hospital with gangrene of the remaining leg is definitely less than for his first admission. The average totals are forty-eight and six-tenths days for the first admission and thirty-three days for the second. The greater safety of the second amputation, the greater life expectancy and the optimistic letters written by many of the patients who have had bilateral amputations, particularly if they have a happy home life, make one feel that the tragedy of diabetic gangrene is not amputation of the

second leg but loss of the first one. It is probable that the reasoning which prompts most surgeons to postpone amputation of the remaining extremity as long as the patient's endurance will permit is based on false premises. May it not be that the second amputation should be advised after a shorter rather than a longer trial of conservative treatment?

Deaths in the Hospital.—Nine and five-tenths per cent of all patients treated for gangrene in its incipient or advanced stages have died in the hospital. Four and six-tenths per cent of the patients treated

TABLE 6.—*End Results After Amputation for Gangrene in One Hundred Consecutive Cases (New England Deaconess Hospital, 1923-1930)*

Present Condition	Number of Patients	Duration of Life, Months	
		Average	Mean
Dead			
No gangrene of other foot	55		
Gangrene of other foot but no operation	19	37.5	
Gangrene of other foot followed by 2d amputation	18	73.3	69.5
Total	92	44.5	37.5
Living			
Bilateral amputation	4		
Trouble with other foot	1		
No trouble with other foot	2		
Total	7	133.6	138
Untraced	1		
	100		

TABLE 7.—*End Results After Amputation for Gangrene in One Hundred Consecutive Cases (Bilateral Gangrene, New England Deaconess Hospital, 1923-1930)*

Gangrene of other foot	41
Average interval from discharge to onset	27.7 months
Average age at first operation	63.2 years
Average duration of life after first operation*	73.3 months

* Four patients are still living and therefore are not counted.

without operation have died. In table 5 are listed conditions which, in our judgment, were responsible for the deaths of these patients. Our early insistence that amputation, once definitely indicated, must be done with a minimum of delay if the patient is to remain in the hospital has done much to minimize the number of patients dying of infection. However, introduction of the guillotine amputation in 1927 and gradual extension of the indications for its use during the next few years have been largely responsible for maintaining the mortality from infection at consistently less than 5 per cent during the past six years (chart 1). Our greatest problem is still presented by the deaths, many of them sudden,

which are due to degenerative changes in the heart and arteries, to pulmonary embolism or to sepsis and disease of the urinary tract.

Late Results.—The first 100 consecutive patients to leave the hospital after major amputations for gangrene have been followed carefully (table 6). Early cases have been selected for this study, because only when all of the patients are dead can their disease be truly understood. Four of the 7 patients known to be living have had double amputations;

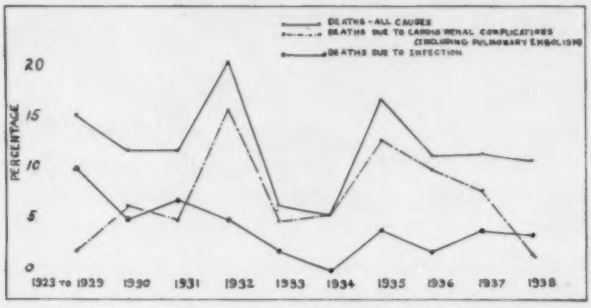

Chart 1.—Yearly mortality from 1923 to 1939, showing the variation from year to year and the relative importance of cardiovascular conditions and infection.

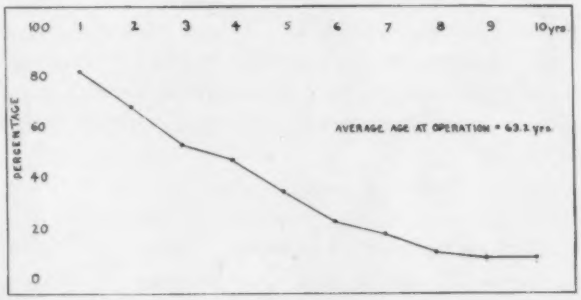

Chart 2.—Survival rate for 92 consecutive patients who died after amputation for gangrene.

1 patient is untraced. The others are dead. Fifty-five per cent of these patients were alive at the end of three years, and only 37 per cent were living five years after operation (chart 2). The average postoperative duration of life for the 92 patients who died was forty-four and one-half months. Forty-one per cent have had either gangrene of the other extremity, which was a factor in their death, or an amputation of the remaining leg (table 7). The average interval between discharge from the hospital and onset of gangrene on the other side was twenty-seven and seven-tenths months. It is of interest that the average postoperative

duration of life of the patients who died after a single amputation was thirty-seven and one-half months, while for patients who are dead at the time of writing but who had bilateral amputations it was seventy-three and three-tenths months.

This study and our experience with amputation of the remaining leg for gangrene suggest that the incidence of bilateral gangrene in diabetic patients who have had one leg removed for obliterative arterial disease is about 40 per cent, that the mortality of the first amputation is nearly twice that of the second and that patients who accept bilateral amputation may look forward to nearly twice the life expectancy of the others.

The physical as well as the economic future of the diabetic patient who has had an amputation for gangrene is not pleasant to contemplate. These as well as the immediate hazards of the disease should be kept constantly before the surgeon as a stimulus to simplify the management of these patients and to minimize the duration of hospitalization.

Refusal of Operation.—As has been stated, it has been our policy to insist on the discharge from the hospital of any patient with gangrene who refuses operation when in the judgment of our group amputation seems indicated. Realizing the seriousness of such a policy, we have followed carefully all patients who have left the hospital against advice. In several instances the trails of these patients seeking relief had to be followed to various cities in New England and not infrequently to New York city. When one realizes that in the thirteen years prior to Jan. 1, 1939, only 33 patients have refused amputation, one cannot but be impressed with the confidence which group discussion and group study inspire in a patient.

The end result is known for all of the 33 cases.[11] Eleven patients survived later amputation of the extremity; 20 died either of progressive gangrene or after amputation elsewhere; 1 had slow healing but has never been able to walk on his foot; 1, who does not strictly belong to this group but is included because amputation was recommended as the procedure of choice, had gradual healing and died four years later of coronary thrombosis. I only wish it were possible to include data on the financial sacrifice made by the families of these unfortunate persons in their vain endeavor to accomplish the impossible.

SUMMARY

The organization at the New England Deaconess Hospital for the care of patients with diabetes mellitus and a gangrenous lesion of an extremity is described.

11. Twenty-five of the 33 patients were women.

Nine hundred and seventy-two cases of obliterative vascular disease in patients with diabetes mellitus are reviewed.

The sex distribution was about equal. The average age was 64.3 years. The average duration of diabetes was eight and seven-tenths years. The mortality in the hospital was 9.4 per cent. The mortality after major amputation was 13.9 per cent.

The causes of death in 73 fatal cases are discussed.

A comparison is given of the results following the use of silk and catgut sutures in 112 consecutive primary supracondylar amputations.

One hundred consecutive patients who left the hospital after a major amputation for gangrene have been followed. The incidence of gangrene of the other extremity, the survival rates and the average postoperative duration of life are given.

The end results in the cases of 33 patients who left the hospital after refusing amputation are given.

RECENT ADVANCES IN ANESTHESIA—1939

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With the passing of each successive year, many additions to the rapidly expanding field of anesthesia are made. The past year has added its share of developments. Although there has been but slight advance in the development of new anesthetic agents which are superior to older agents, valuable advances in the use and application of older agents and methods have been made. With inhalation and regional anesthesia still holding their place among the standard methods, intravenous anesthesia has made a progressive advance. Its increased usefulness has been apparent throughout the United States, and its promising possibilities are being fulfilled. Advances in local, spinal, inhalation and intravenous anesthesia will be considered individually, but before this is done a consideration of other methods is in order.

Rectal anesthesia still holds a place in selected cases, but its use is not as prominent as heretofore. Ether in olive oil is still much employed for obstetric anesthesia and analgesia but is now little used in general surgery. Tribromethyl alcohol in amylene hydrate (avertin with amylene hydrate) is still extensively employed as a basal rectal anesthetic and fills a useful place. However, to be thoroughly safe it should be used only to produce basal narcosis and not as the sole anesthetic agent. Many anesthetists prefer to administer one of the barbiturates orally, rectally or intravenously for preanesthetic medication in preference to other, more complicated basal anesthetic agents administered by rectum.

As young children possess a relatively high tolerance to the rectal administration of tribromethyl alcohol in amylene hydrate (avertin with amylene hydrate), the use of this anesthetic is often of advantage. This is true particularly in certain operations and manipulations about the respiratory passages. As an example, one may cite the removal of a foreign body from the trachea or esophagus of a young child. The rectal administration of this agent usually produces sufficient anesthesia for completion of the procedure. Too deep a narcosis is not desirable,

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From the Section on Anesthesia, the Mayo Clinic.

and it is safer to maintain the pharyngeal and laryngeal reflexes to a certain degree. The average dose ranges between 80 and 100 mg. per kilogram of body weight; the dose may be increased slightly if the child is particularly robust. The solution should be instilled about ten minutes prior to the manipulation. The fact that the child is not completely relaxed and may cough or strain at times is not of particular disadvantage to the surgeon; when these signs are present the child will barely be overdepressed. Equipment for administration of oxygen and for maintenance of a free airway should always be available.

The barbiturates continue to be useful as basal narcotics for rectal administration. When persistent vomiting is present or when the patient is psychotic and refuses medication by mouth, the rectal route may be employed. A longer-acting barbiturate, such as sodium amytal (sodium isoamylethylbarbiturate), is preferable if prolonged sedation is desired; if a shorter period of sedation is required, pentobarbital sodium or one of the shorter-acting barbiturates will be adequate. One of the shorter-acting barbiturates will be more desirable for use as a preanesthetic medicament. The rectal method of administering barbiturates is particularly useful for the sedation of young children. Pentobarbital sodium administered half an hour prior to the giving of a blood transfusion to a child renders him quiet and amenable to the procedure. Usually he will rouse only during the venipuncture, and he will sleep quietly during the infusion. Such sedation makes administration of a transfusion to an infant or a young child much easier to accomplish, and the child seldom remembers the occurrence. Children tolerate pentobarbital sodium well, and those as young as 1 year of age may be given 1½ grains (0.1 Gm.). If there is any doubt as to the amount to employ, a smaller dose—for example, ½ grain (0.032 Gm.)—should be given and repeated until the desired effect is obtained. The easiest method of administering pentobarbital sodium by rectum is in a capsule, which should be punctured several times with a pin prior to insertion to hasten solution and absorption. If desired, a solution of the drug may be made up and instilled into the rectum or the drug may be administered in the form of a suppository.

Adequate preliminary medication is essential prior to inhalation, local, spinal or intravenous anesthesia. The agents still most frequently employed for this purpose are morphine and atropine administered subcutaneously and a barbiturate administered orally, rectally or intravenously. Some physicians prefer to employ scopolamine instead

of atropine. Premedication is begun the night before operation; at this time, 1½ grains (0.1 Gm.) of pentobarbital sodium is administered orally. The following morning an additional 1½ to 3 grains (0.1 to 0.2 Gm.) of pentobarbital sodium is administered by mouth about an hour and a half before the operation. One half to three quarters of an hour before the operation, ⅙ grain (0.01 Gm.) of morphine sulfate and 1/150 grain (0.00043 Gm.) of atropine sulfate are given by hypodermic injection. The dose of the various agents will vary with each patient, depending on the degree of excitability and on whether or not the condition of the patient contraindicates the use of one or more of the agents.

Endotracheal intubation becomes more and more useful as time goes on, both as an adjunct to anesthesia and for purposes of resuscitation. The Magill type of curved, soft rubber catheter continues to be the apparatus of choice. For resuscitation, a rigid or semirigid tube may have advantages in certain cases in which intubation is difficult, or the Magill tube may be inserted by means of an obturator to give the endotracheal catheter added rigidity. Catheters with inflatable cuffs are used in certain instances (for example, in some intrathoracic operations) and when a leakproof system cannot be otherwise maintained. Ordinarily, this may be accomplished by means of a moist or petrolatum gauze pack placed firmly in the oropharynx, around the endotracheal catheter. Endotracheal intubation is not performed routinely in general surgical procedures with inhalation anesthesia but is reserved for use in cases in which a free airway may not be otherwise obtained. Intubation is most frequently carried out prior to the beginning of the operation if the proposed procedure is on the upper part of the abdomen, if it is to be long or extensive or if the patient is frankly a poor risk and complications are anticipated. Most intracranial operations and extensive operations about the head and neck continue to be performed under endotracheal anesthesia.

Pyrex glass tubes, formerly used to protect the endotracheal catheters and maintain them in a clean or sterile condition, have been superseded by transparent, unbreakable plastic cases curved to the shape of the catheter. Whether both the endotracheal catheters and their plastic cases are to be maintained in a sterile condition is a matter of individual preference. In any event, the casing serves the purpose, protects the catheter from any gross contamination after it has been boiled, protects it from injury and prolongs its life. These plastic cases are light and durable and seldom need to be replaced. Although they are not resistant to boiling, to autoclaving or to the action of sterilizing agents containing

alcohol, they may be safely sterilized in aqueous solutions of metaphen (the anhydride of 4-nitro-5-hydroxymercurioorthocresol) or merthiolate (sodium ethylmercurithiosalicylate).

INTRAVENOUS ANESTHESIA

Although no new agents possessing outstanding merit as intravenous anesthetics have been evolved during the past year, certain improvements and advances have been made in the method of administration and scope of the agents already in use. The most reliable and satisfactory agents in use at present for this purpose, as has been previously reported, are the short-acting barbiturates pentothal sodium (sodium ethyl-1-methyl-butyl thiobarbituric acid) and evipal sodium (sodium n-methyl-c-c-cyclohexanolmethyl barbituric acid). Both produce effective and satisfactory anesthesia when administered by the fractional method of injection. Their use is safe only in the hands of competent anesthetists who are aware of the dangers and contraindications. The technic of administration, the effects and the scope of action of these two agents run parallel, and each fills a useful place. Pentothal sodium is the more potent of the two; it produces better anesthesia, and somewhat smaller doses are required. One of the most important advances in intravenous anesthesia is the reduction in concentration of the solution to be injected. During the past few years the concentration has been reduced from 10 per cent to 5 per cent, and it has now been further reduced to 2.5 per cent. This concentration is felt to be the optimum for a number of reasons. Since pentothal sodium in 2.5 per cent solution has been employed, the incidence of delayed phlebitis has been reduced to practically nil, as has that of other forms of venous irritation following its use. Should extravenous injection of such a dilute solution occur, the irritating effect on the tissues would be slight and transient. Although a larger volume of solution must be injected than would be necessary if a more concentrated solution were employed, the resultant anesthesia is just as effective. With use of a 2.5 per cent solution, smaller total doses have seemed to be employed, and there is less tendency, particularly for the beginner, to give larger doses than are actually required. Thus, a wider margin of safety is attained.

The scope of intravenous anesthesia has also been widening, and the types of operation for which it may be used to advantage have increased. The fact that it is a method which excludes the hazard of fire and explosion is one factor which accounts for its increasing use. Improved methods of administration are another. Minor operations in all fields of general and special types of surgery have been performed

for some years with the use of intravenous anesthesia; longer and more extensive operations are now being done. This has been accomplished largely through the use of suitable supplementation of the intravenous method. Local and regional anesthesia, which has been employed for some time for this purpose, reduces the amount of the barbiturate necessary to produce satisfactory anesthesia. Certain abdominal operations may be performed with safety by using such a combination.

Intravenous anesthesia is increasing as a supplement to spinal anesthesia when the latter is inadequate or is beginning to wear off or when nausea or straining is present. It is well to inject the barbiturate very slowly and cautiously if the patient has been given a spinal anesthetic; otherwise, overdepression of a respiratory function already depressed by the spinal anesthetic may result.

In certain cases even excessive amounts of the barbiturate fail to produce adequate anesthesia. It is unwise to continue giving such large doses. Lundy has suggested intravenous administration of morphine as a supplement in such instances. The syringe containing the barbiturate is removed from the intravenous needle, which is left in the vein. A syringe containing ⅙ grain (0.01 Gm.) of morphine sulfate in 3 cc. of physiologic solution of sodium chloride is attached to the needle, and small fractional doses of the morphine are administered. Throughout the injection the patient is carefully watched for signs of an untoward effect. The dose administered depends on the condition of the patient and the reactions observed. It may vary from 1/24 to ⅙ grain (0.0027 to 0.01 Gm.). On completion of the injection of morphine, the syringe containing the barbiturate solution is again attached to the needle, and administration of the latter drug is continued. The usual result is that the patient reacts favorably to subsequent doses of the barbiturate, and average doses then produce adequate anesthesia.

Administration of oxygen from the gas machine during induction of intravenous anesthesia permits the carrying out of more extensive operations than could otherwise be safely accomplished. This is especially true of certain abdominal operations. The effect of the oxygen is toward better relaxation when less of the barbiturate is used. Cyanosis caused by respiratory depression does not occur unless the airway becomes obstructed. The use of oxygen permits better minute to minute control, and the movements of the breathing bag provide information in regard to respiratory exchange. Such a method also permits the addition of nitrogen monoxide to the oxygen for patients who require a large amount of the barbiturate. Administration of 50 to 70 per cent nitrogen

monoxide in oxygen to patients of this type materially decreases the total amount of intravenous anesthetic necessary without increasing the danger of anoxia. This combination is 100 per cent fireproof and explosion-proof and permits the free use of the cautery, diathermy or other electric apparatus. Even with these supplements, extensive abdominal operations with intravenous anesthesia are hardly justified.

The use of intravenous anesthesia for certain types of operations on the larynx has proved to be another advancement. In the past, operations for lesions on or about the vocal cords with the use of direct laryngoscopic procedures were performed with the patient under deep ether anesthesia. Intravenous anesthesia was felt to be contraindicated. Ether anesthesia, although satisfactory, carried with it certain disadvantages. To obliterate the laryngeal reflexes the anesthesia had to be carried to a deep plane, necessitating the use of large quantities of ether. As a result, the period of recovery was prolonged and there was much nausea and vomiting. This was out of proportion to the duration of the operation, which often takes only a few minutes. Certain modifications in the technic of intravenous anesthesia are necessary to the successful handling of patients by this method. Before the patient is placed on the operating table, the pharynx and the region of the glottis and epiglottis are thoroughly cocainized by topical application of a 10 per cent solution of cocaine hydrochloride until the reflexes are obliterated. As soon as induction of intravenous anesthesia is complete, the glottis is visualized, and further cocainization of the vocal cords is carried out if necessary. Before the operation is begun, a pharyngeal tube is passed by the nasal route and is connected to the gas machine for the purpose of delivering oxygen intrapharyngeally to the patient. With such a sequence it is not necessary to maintain too deep a plane of anesthesia. Ether presents some fire hazard, as the electrocautery is used frequently in the treatment of lesions in this region. This danger is completely excluded by the use of intravenous anesthesia. The period of recovery is shortened, and the patient is saved much postoperative discomfort. The tendency to postoperative pulmonary complications is lessened.

Bronchoscopic or esophagoscopic examination of certain nervous and apprehensive patients may be performed in a similar manner. The chief variation in technic is that after induction of anesthesia and introduction of the instrument, administration of the anesthetic agent is discontinued, and additional doses seldom are required. The patient may attempt to cough and strain, but this is of little moment to the surgeon, who is accustomed to working under such conditions. As a result of

this technic, the patient is reacting vigorously by the time the examination is complete and is able to cough up blood, pus or mucus which might otherwise cause obstruction. On the other hand, if deep anesthesia is maintained throughout the operation, mechanical obstruction to respiration may follow removal of the laryngoscope; this is abetted by the loss of stimulus to the laryngeal reflexes following removal of the instrument.

Such procedures are highly technical, and the use of intravenous anesthesia for them is safe only in the hands of anesthetists who are widely experienced in these specialized methods.

The importance of intravenous anesthesia in military surgery has never been as fully realized as at present. The ease of transporting the simple equipment required adds to the value of the method. As the solutions are relatively stable for periods ranging from twenty-four to forty-eight hours provided they are not exposed to light and air for prolonged periods, sufficient solution for several administrations may be made up in a 500 cc. bottle equipped with a sterile rubber stopper. Syringes may be filled as needed by piercing the stopper with a suitable needle.

INHALATION ANESTHESIA

Inhalation anesthetic agents and methods have shown little change during the past year. Despite advances in other fields of anesthesia, inhalation methods continue to be of major importance. Ether remains as useful as ever and continues to hold its place as the safest anesthetic for general administration. Although ether is now administered largely by means of the gas machine in combination with oxygen and other gases, the usefulness of the drop method should not be overlooked. This method still has wide application, owing to its simplicity and its safety, particularly in the hands of surgeons of limited experience. Divinyl ether and ethyl chloride still enjoy a limited field of application in some sections of the United States. Among the gaseous agents, nitrogen monoxide, ethylene and cyclopropane all continue to be extensively employed. The carbon dioxide absorption technic of administering these agents with oxygen and with or without the addition of ether remains in almost universal use. The reliability of nitrogen monoxide for induction followed by administration of ether by the closed method is attested by the high percentage of cases in which this method is employed. Of the three aforementioned gaseous anesthetic agents, nitrogen monoxide only is nonexplosive. In the light of the anesthetic explosions that have occurred in the past year in cases in which cyclopropane was being used, many anesthetists have adopted a conservative

attitude toward its use. Most of these explosions have been attributed to ignition of the explosive mixture by electrostatic spark. Many different attitudes in regard to the use of cyclopropane have arisen from these occurrences. Some anesthetists continue to employ it as previously; others, while continuing to use it, have adopted methods of electric intercoupling of the anesthetists, the patient, the gas machine and the operating table to disseminate accumulated electrostatic charges, and still others feel that its use should be limited to cases in which it is definitely indicated. Those who favor the last-mentioned practice do not keep a tank of cyclopropane on the gas machine but place the tank on the machine for use only during the duration of anesthesia in the selected cases.

Examples of suitable procedures might include operations for intrathoracic tumors, lobectomy or pneumonectomy and operations for diaphragmatic hernia. This agent may be used also in certain cases of infection of the respiratory tract in which inhalation anesthesia appears to be indicated. Cardiac irregularities occurring in the course of cyclopropane anesthesia have received more attention in recent months than formerly. Cyclopropane is of definite value in certain cases, but its dangers must always be borne in mind.

LOCAL, REGIONAL AND SPINAL ANESTHESIA

Procaine hydrochloride continues to head the list of local anesthetic agents owing to its comparatively low toxicity and wide margin of safety. This applies to all forms of local and regional, including spinal, anesthesia. The use of metycaine, among other local anesthetic agents, continues to increase. Its longer duration of action, dose for dose, as compared with procaine hydrochloride often makes it the agent of choice for the blocking of nerve trunks and plexuses as well as for producing spinal anesthesia for operations lasting more than forty-five minutes. As the technic of its administration is identical with that of procaine except for a 10 to 20 per cent reduction in the dose, it serves as a valuable alternative local and spinal anesthetic agent for robust persons. Pontocaine hydrochloride continues to be favored by some physicians as a spinal anesthetic for prolonged operations on the lower part of the abdomen and on the pelvis. Certain workers combine dextrose with pontocaine hydrochloride to aid in controlling the level of anesthesia. The use of peridural anesthesia remains limited, and the results obtained with this type of anesthesia cannot yet be said to be consistent and reliable.

Local anesthesia has been employed as a supplement to intravenous anesthesia to the advantage of both methods, and by the use of such a combination the scope of both methods has been broadened. Standard blocks, such as sacral block, cervical block, block of the brachial plexus and paravertebral block, are employed as frequently as in the past, although intravenous anesthesia now supplants regional anesthesia in certain cases or is used to supplement the latter method. The use of diagnostic and therapeutic nerve block appears to be generally on the increase.

Spinal anesthesia would appear to have become adjusted to its level of usefulness. While some surgeons continue to favor its use for operations on the upper part of the abdomen, it is employed more often for operations on the lower part. The lower the level of spinal anesthesia required, the safer the method becomes. Ephedrine continues to be widely used for vasopressor purposes. The usual dose of ephedrine is 25 mg. administered prior to the injection of the spinal anesthetic agent. Should an additional dose be required, intravenous administration is to be preferred, as subcutaneous or intramuscular administration produces an inadequate effect. Neo-synephrin hydrochloride continues to be promising as a vasopressor agent in spinal anesthesia.

Introductory Note

SYMPOSIUM ON PROTRUDED INTERVERTEBRAL DISKS

This group of papers on protrusion of intervertebral disks is presented in an attempt to bring up to date the knowledge of this definite pathologic and anatomic condition, which has in years past for the most part gone unrecognized and which results in untold suffering and accounts for a tremendous economic loss because of the incapacity of persons so affected.

These papers are not a collective study, for there has been no pooling of statistics and each author has been requested to write from his own experience and to state the conclusions which he has reached with regard to this intriguing, important and timely problem.

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